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1. Hock, C. W.: J. Med. Assn. Ga. 40:22, 1951. 2. Hufford, A. R.: J. Mich. St. Med. Soc. 49:1308, 1950. 3. Chamberlin, D. T.: Gastroenterology 17:234, 1951. 4. Pakula, S. F.: Postgrad. Med. 11:123, 1952.

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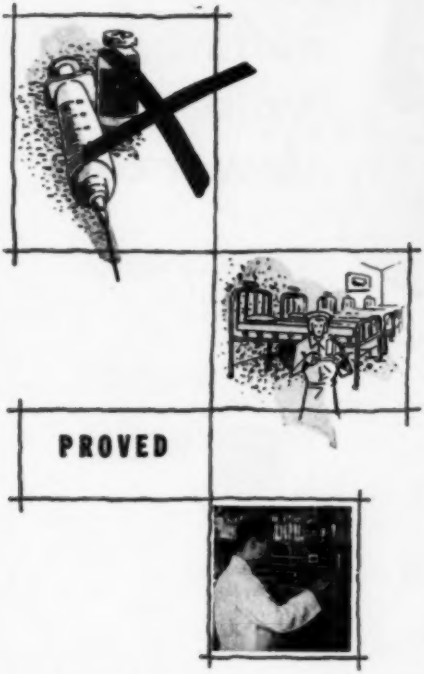

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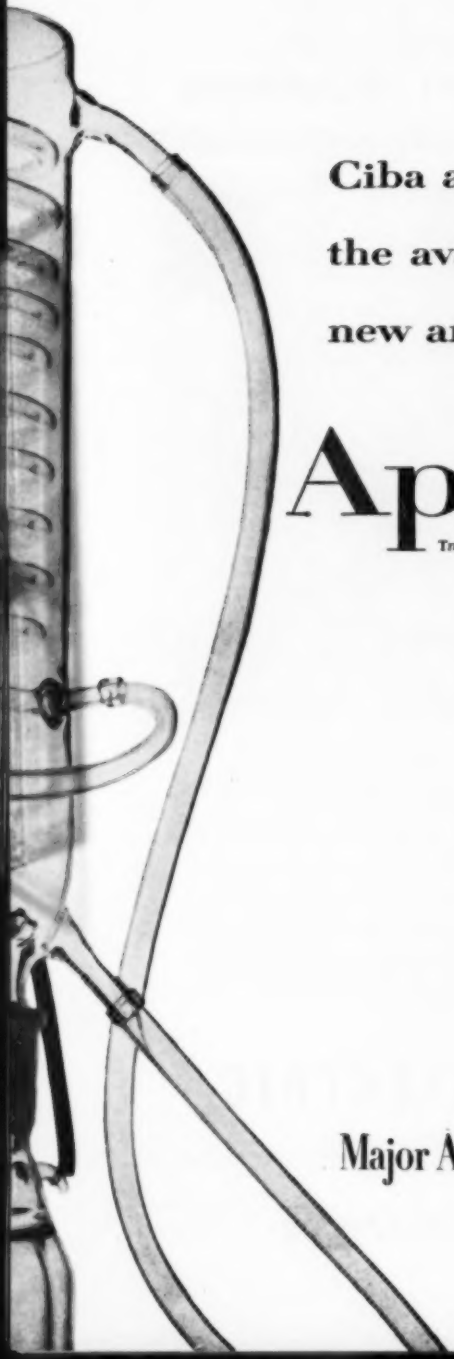
*Cronheim, G., Justice, T. T., and King, J. S., Jr.. A New Approach to Increasing Tolerance of Oral Aminophylline–to be published.

*Justice, T. T., Jr., Allen, G., and Cronheim, G., Studies with Two New Theophylline Preparations–to be published.

**Waxler, S. H. and Schack, J. A., Administration of Aminophylline, J. A. M. A. 143:8, 736-739, June 1950 (This study does *not* refer to Aminodrox.)



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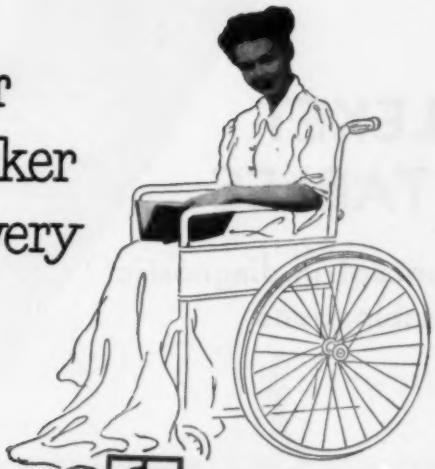

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*Spies, T. D.: Rehabilitation Through Better Nutrition, Philadelphia, W. B. Saunders Co., 1947, p. 89.

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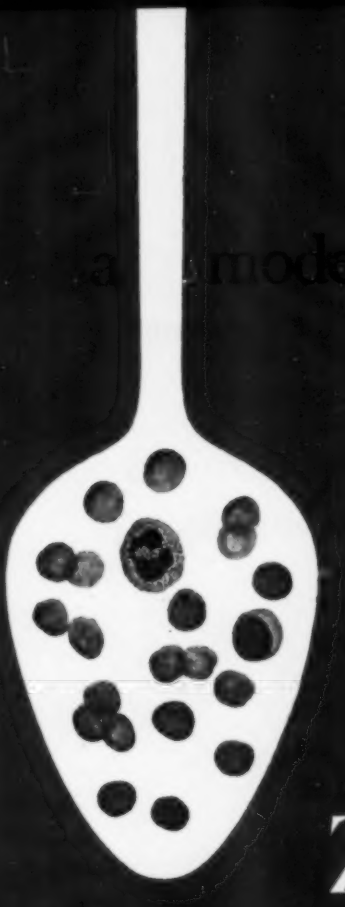

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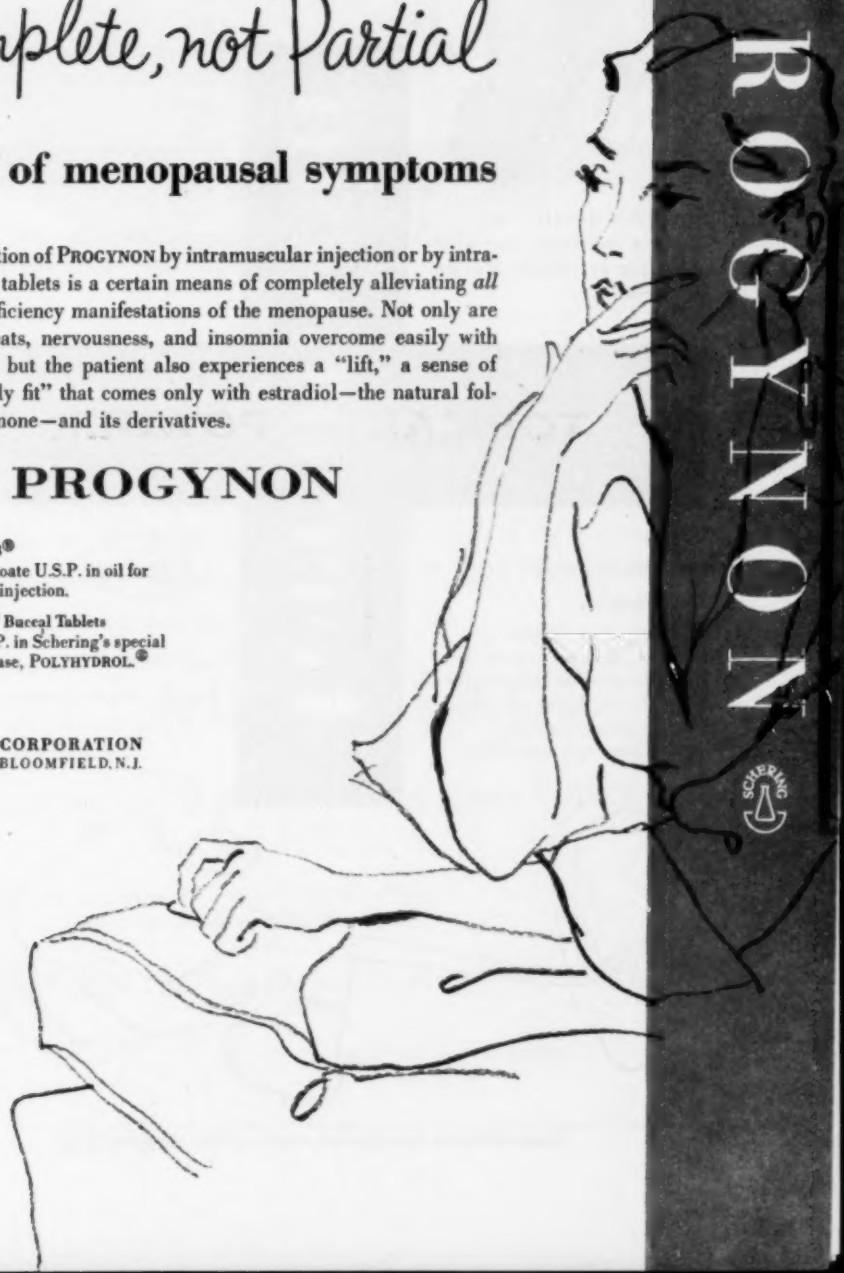

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ANNALS OF
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VOLUME 36 MAY, 1952 NUMBER 5

MÉNIÈRE'S DISEASE: ITS PATHOLOGIC FEATURES, CLINICAL EXPRESSIONS AND THERAPY *

By MAURICE SALTZMAN, M.D., *Philadelphia, Pennsylvania*

MÉNIÈRE [1] discovered, at autopsy, an inner ear lesion which afforded an explanation for a symptom complex he had observed during the patient's last illness. A summary of the case history follows:

A young woman was seized with sudden vertigo, nausea, vomiting, tinnitus and deafness. The attack lasted five days, terminating in death. At autopsy, the brain and spinal cord disclosed no abnormality. The histologic study of the inner ear showed the perilymph spaces of the semicircular canals and vestibule to be filled with a reddish plastic exudate as a result of a recent hemorrhage. The cochlea was uniquely uninvolved.

A clinicopathologic report, nearly an exact duplicate of the Ménière case, was presented by Hallpike and Harrison [2] recently. Their patient was seized with an attack featured by vertigo and vomiting 17 days prior to her death. Four days after the initial attack, she developed tinnitus of the character of "a threshing machine going all the time." Bilateral hearing impairment was also present. Histologically, there was evidence of recent hemorrhage in all parts of the inner ears except the scala media, which appeared conspicuously intact on both sides. As this patient was suffering from myelogenous leukemia, the hemorrhagic infiltrations of the labyrinths consisted of red cells and leukemic cells which corresponded to their proportions in the blood stream.

It is noteworthy that in these cases, the ductus cochlearis was alone intact, while the hemorrhagic lesion involved the remainder of the labyrinths. Leukemia was a predisposing factor in Hallpike and Harrison's patient. Druss [3] found involvement of the inner ear, as evidenced by nerve deafness,

* Presented before the Section on General Medicine of the College of Physicians, Philadelphia, May 28, 1951. Received for publication October 19, 1951.
From the Department of Oto-Rhinology, Temple University School of Medicine.

vertigo and nystagmus, in 6 per cent of the 148 cases of leukemia admitted to the Mount Sinai Hospital during the years 1929–1934.

The symptom complex of vertigo, tinnitus and deafness, of unknown etiology, which is never fatal, is generally termed "idiopathic Ménière." Its histopathology was described by Hallpike and Cairns [4] in 1938. The scala media or ductus cochlearis was found grossly dilated by an increased amount of endolymph.

The exact composition of normal perilymph and endolymph is unknown. Waltner and Raymond [5] studied five specimens of perilymph from individuals with Ménière's disease and one specimen of endolymph from a Ménière patient. The perilymph was collected when the Day operation was performed, while the sample of endolymph was obtained at the tearing of the endolymphatic duct during a Portmann operation. Measurements of the ultraviolet absorption and total nitrogen were made on these fluids, and it was found that the protein content of the Ménière inner ear fluids was more than twice that of the cerebrospinal fluid of the same patients. The perilymph and endolymph had an identical protein concentration. In one perilymph specimen, the sodium content was determined and was found to be similar to that of the cerebrospinal fluid.

Altmann and Waltner,[6] Gisselsson [7] and Waltner [8] have proved experimentally that the membranes of the inner ear are semipermeable—that they do not permit the passage of large molecules of colloids but that crystalloids diffuse through these barriers readily. In a recent paper, Altmann and Waltner [9] state that under normal physiologic conditions the direction of movement of dissolved substances is from the endolymph towards the perilymph. Now, on finding hydrops of the cochlear duct in Ménière's disease, we must assume that in this condition an osmotic gradient in favor of the endolymph exists. While Waltner and Raymond's [5] study demonstrated an almost identical index of refraction and total nitrogen of the endolymph and perilymph in Ménière's disease, these findings represent the end result of the equalization of the osmotic pressure on both sides of the barrier membrane between the endolymph and perilymph spaces. It is a logical deduction that during the moments of the formation of the endolymphatic hydrops, there existed a special factor that augmented the osmotic pressure of the endolymph, causing the movements of fluid in the direction of the ductus cochlearis.

Other histologic findings in idiopathic Ménière include deformity of the utricle, dilatation of the saccule, degenerative changes in the organ of Corti, and the presence of albuminoid coagula in the semicircular canals.

Clinical Picture

The symptoms in idiopathic Ménière may be transitory. Sometimes only minor functional changes may be discernible after one attack. Reflected in the pathologic mirror, this would indicate that degeneration of the neuro-

epithelium of the inner ear does not necessarily follow the upsurge of endolymphatic hydrops. Again, the devastating effects of an attack may not fall uniformly on the several parts of the inner ear. Most frequently, the cochlea bears the brunt of the attack.

Brunner [10] reports that in 52 per cent of his Ménière cases the symptom complex was incomplete, the attacks being characterized by labyrinthine features in some, while others showed only cochlear disturbances. He divides these attacks into the labyrinthine type and the cochlear type. He cites the case of a man, aged 34, in whom the vertiginous attacks were the only disturbing manifestations for three years prior to the onset of tinnitus and deafness to complete the Ménière symptom complex.

It is an accepted fact that the Ménière labyrinth is frequently hyposensitive or nonresponsive to Bárány stimulation. Therefore, in a given case of "labyrinthine type" of Ménière's disease in which vertigo is the only complaint, and negative responses to turning and douching are the outstanding features, there will arise a problem in the differential diagnosis. In discussing the patient with vertiginous attacks, Jones and Fisher [11] say, "A central lesion is suggested by a normal cochlea, but impaired or non-responsive semicircular canals." If the labyrinthine type of Ménière's disease may give a similar symptom complex, the differential diagnosis must depend upon the other neurologic findings, whether they point to a peripheral or a central lesion.

The cochlear type of Ménière's disease was described by Williams and associates [12] and Brunner.[10] Deafness was the cardinal symptom, and there was no history of vertiginous attacks in these cases.

The complete Ménière symptom complex includes a history of a solitary vertiginous attack or recurrent attacks, a sudden onset of a hearing impairment which may be unilateral or bilateral, and tinnitus aurium. Spontaneous nystagmus is invariably manifest during a genuine attack. It is usually rotary but may be horizontal; it is rarely vertical. The direction of the nystagmus is toward the affected ear if the labyrinth is in the irritative stage of the disease. On the other hand, the direction of the nystagmus is toward the uninvolved side if degenerative changes are present in the affected ear. As the pathologic state of labyrinth varies, the patient will find more comfort while lying on the side which falls in the plane of the direction of his nystagmus. Accordingly, the patient who has gone through a genuine Ménière attack will give a history of having found relief by lying on one side, and having experienced greater discomfort in the attempt to turn over to the other side. Usually, nystagmus disappears with the cessation of the attack. During the attack, the patient experiences a sensation of turning—either that his body rotates around its long axis or that visible objects are turning in front of his eyes. Recurrences take place in episodes at variable intervals—days, months or years. Between attacks, tinnitus and fluctuating deafness are the only residual symptoms.

In a lesion of the brainstem, the complaint is most often "dizziness"—not rotational vertigo—and some suggestive neurologic signs are continuously present. A cerebellopontine angle tumor gives vertigo, deafness and tinnitus, but there is also a loss of the corneal reflex, hypesthesia of the face, incoördination, weakness of the facial muscles and paresis of the lateral rectus. Headache and vomiting are commonly present. Hoarseness and difficulty in swallowing appear late in the disease. The Bárány findings in an angle lesion are pathognomonic—a "dead" labyrinth on the affected side and no responses from the vertical canals on the opposite side. Thrombosis of the posterior inferior cerebellar artery causes nystagmus and vertigo, but the distinguishing features are marked incoördination, ipsilateral hypotonia, staggering, Horner's syndrome, loss of corneal reflex, hoarseness, difficulty in swallowing, ipsilateral absence of temperature and pain sensation to the face, and a loss of these sensations on the contralateral side of the body.

Tinnitus, in Ménière's disease, is quite characteristic. It has dual tonal properties—a high pitch which, comparatively, is not troublesome, and a low pitch that is most disturbing.

The cochlear pathology gives characteristic psychophysiologic features. Diplacusis is frequently present. Due to an overabundance of recruitment, there is poor tolerance of loud sounds. Speech intelligibility is poorer than pure tone acuity. Deafness is fluctuating. Most often there is greater hearing impairment soon after an attack, while a lengthy intermission allows considerable recovery to take place. Poor bone conduction is a constant finding. The hearing impairment is of sudden onset and frequently shows a severe involvement of the low tones.

A "nerve-deafened" ear gains in loudness disproportionately with an increase of an increment of intensity. This special function has been termed the "recruitment phenomenon" by Fowler.[13] Accordingly, loud sounds may be heard by some "nerve-deafened" ears with a degree of loudness which is equal or nearly comparable to the sensation of loudness with which the normal ear would perceive them. Dix, Hallpike and Hood [14] studied 30 patients with Ménière's disease and found marked loudness recruitment in every case. Subsequently, these authors [15] reported the paradoxic finding that speech intelligibility may be absent in Ménière's disease despite the presence of the recruitment phenomenon. Saltzman and Ersner [16] obtained comparable results in their loudness function and speech intelligibility determinations of Ménière patients. In a quantitative study, they found that advanced Ménière cases had poorer speech hearing than pure-tone acuity, and that speech intelligibility may be entirely absent in an occasional case.

A composite audiogram, containing pure-tone curves and bar-graphs of speech intelligibility, constitutes a most important diagnostic criterion.

It also follows that such repeat audiograms may serve as yardsticks with which to measure improvement due to therapy.

Figure 1 is the audiogram of a patient with Ménière's disease—advanced in the left ear and early in the right ear.

A psychosomatic syndrome resembling Ménière's disease is encountered clinically. There is a history of vertigo and ringing in the ears, but the patient also states that he has tingling and numbness in the hands and feet.

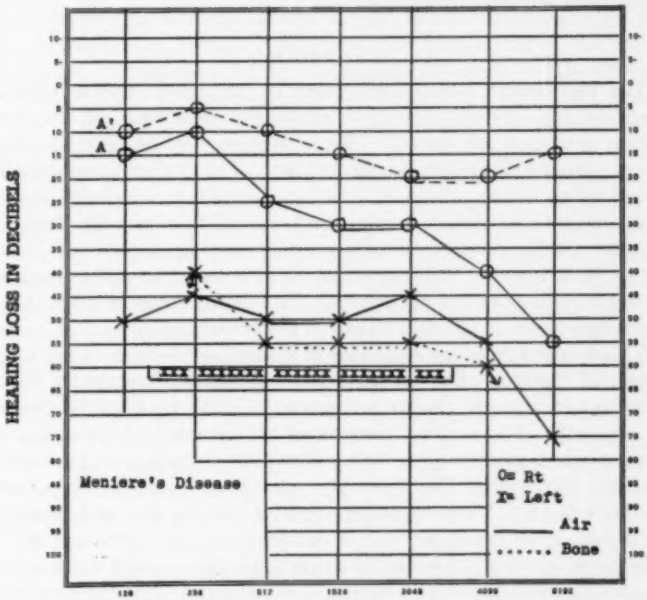

FIG. 1. *Right ear*—early Ménière's disease. Curve A taken immediately following an attack. Curve A' taken after an intermission of two months. Speech intelligibility in the right ear was practically normal. *Left ear*—advanced Ménière's disease. Bone conduction is poor. Bar with crosses indicates the threshold of intelligibility for spondee words in the left ear.

There is no let-up, according to the history, and the attacks are becoming more frequent. The feeling of "going to pieces" is complained of. In the absence of deafness, the nature of the condition is readily discerned. A diagnostic problem arises when a patient with organic deafness develops an anxiety neurosis with tinnitus and vertigo. The audiometric pattern helps in the differential diagnosis.

Another condition which is loosely attached to the inner ear syndromes has been termed symptomatic Ménière by Brunner.[17] Vertigo is the dis-

turbing symptom. Tinnitus may also be present. Etiologically, it does not depend upon a pathologic process in the perilymph or endolymph spaces. It is a symptom complex arising secondary to a lesion elsewhere in the body. It may constitute the aura in epilepsy, and it is frequently a prominent feature in disseminated sclerosis. Other causes are the infections, toxemias of gastrointestinal or renal origin, ocular disease, anemia, cardiac and blood pressure disturbances, avitaminosis, head injury, tabes, blockage of the Eustachian tubes and cholesteatoma. Here again, the audiometric pattern is helpful in the differential diagnosis.

Therapy

The therapeutic avenues for relief in Ménière's disease have become numerous and varied. Dandy [18] advocated sectioning of the vestibular division of the eighth nerve. This operation may be utilized only in the case of extreme disability due to vertigo. The patient is subjected to the hazards of an intracranial operation for a condition which is never fatal in itself. Walsh and Adson [19] state that, in addition to relief from vertigo, a greater amelioration of tinnitus may be obtained by the total sectioning of the eighth nerve. Yet in a series of 11 cases of complete section of the eighth nerve, they report no amelioration from tinnitus in seven cases, complete relief in two and partial benefit in the remaining two.

This fact suggests the existence of a retrolabyrinthine factor in the production of tinnitus. On the other hand, Lempert [20] succeeded in the cure of tinnitus in a vastly greater percentage of cases by a special operation on the labyrinth. His method consists of the removal of the stapes and the round window membrane to bring about degeneration of the entire endolymphatic labyrinth. The operation was performed on 15 patients with Ménière's disease. Twelve became free of both vertigo and tinnitus, while in the remaining three, tinnitus of lessened intensity persisted and vertigo disappeared entirely. Lempert's successful results would indicate that nonhallucinatory tinnitus originates in the inner ear. Then the question arises, Why does the tinnitus persist when its central cable, the eighth nerve, is cut? A plausible hypothesis is that two accessory cables, the seventh and ninth nerves, connect the inner ear to the brain. The tympanic plexus in man contains vestiges of the structures which in primitive animals carry auditory and equilibratory impulses, by way of the seventh and ninth nerves, to the brain stem. Schneider [21] describes this accessory auditory apparatus as the "internal sonic system," which is derived from the lateral line organs of aquatic vertebrates.

In unilateral Ménière's disease, relief from vertiginous attacks may be obtained by decompressing or destroying the external semicircular canal on the affected side. Day [22] begins with a partial simple mastoidectomy by the postauricular route. With a small motor-driven burr, the horizontal canal is opened near its ampulla and a coagulating needle is passed forward

through the canal into the vestibule. A light coagulating current is then used for two or three applications of about one second each. A few sulfonamide crystals are then dusted into the cavity and the mastoid incision is completely closed with clips. Six patients with unilateral involvement, on whom Day carried out this operation, have become completely free of vertiginous attacks. In two patients, the hearing has remained at the same level as before the operation; in one, whose uniform preoperative loss was 70 decibels, the hearing since operation has returned to normal; in three cases, a further loss of hearing, chiefly in the lower tones, followed the operation. According to Wright,[23] however, the destruction of the static labyrinth may be accomplished by a nonsurgical procedure. His method consists of the injection of one minim of alcohol into the perilymph space. The vestibule is entered through the membrana tympani and foot plate of the stapes. It is this part of the labyrinth that one wishes to destroy. Only a small quantity of alcohol is to be injected, since an excessive amount may cause facial paralysis.

When a surgical procedure is advocated, it is in unilateral Ménière with extreme suffering. However, one may question whether there is a reasonable assurance that the condition will remain unilateral. I have seen several cases in which the Ménière symptom complex has been limited to one ear for several years, and then, suddenly, a typical attack occurred in the other ear. In the Mayo series,[19] there were 115 unilateral and 67 bilateral cases.

A medical treatment directed at the cause of the disease would have the added advantage of safeguarding the unaffected ear. Freedom from vertiginous attacks was considered the criterion for improvement from treatment by the earlier investigators. However, as spontaneous remissions occur, a period of freedom from vertigo may be just a coincidence and not necessarily due to the therapy instituted. Mygind and Dedering [24] advise the restriction of fluid and salt intake to combat labyrinthine edema. Physiotherapy to improve the patient's circulation is also advocated by these authors. Furstenberg and associates [25] are of the opinion that Ménière's disease is due to a retention of sodium. Their régime consists of a salt-poor diet and the administration of ammonium chloride. However, their theory is not in keeping with the modern pathologic concept,[26] which holds that an electrolyte disturbance may be a secondary factor in the cause of edema and not a primary one. Talbot and Brown [27] studied the acid-base constituents of the serum of 28 Ménière patients, and no constant variations from the normal were observed. The study included total fixed base, sodium, potassium, calcium, chloride, total carbon dioxide, phosphates, protein and nonprotein nitrogen. Four patients were given massive doses of sodium orally and intravenously without causing an attack. Talbot and Brown's method of treatment consists of the administration of large doses of potassium to improve the conduction of nerve impulses as in familial periodic paralysis and myasthenia gravis.

Atkinson [28] divides his Ménière cases into two groups, the histamine sensitive individuals and the vasoconstrictive ones. On the injection of 0.01 mg. of histamine hydrochloride intradermally, the sensitive person develops a wheal, 1 to 1.9 cm. in diameter, with pseudopods and a surrounding flare of 5 to 6.4 cm. in diameter; whereas the wheal in a nonsensitive individual is smaller and has no pseudopods, and the surrounding flare is less extensive and fades in 10 to 20 minutes. The course of treatment of a histamine-sensitive patient is begun with a dose of 0.01 mg. subcutaneously and is gradually increased twice to three times weekly for a month or longer. In the vasoconstrictive group, the symptoms usually begin at an advanced period of life, the patients being 40 years of age or older. The mechanism by which the membranous labyrinth becomes overdistended with endolymph consists of primary vasoconstriction and anoxemia of the nutrient vessels, and secondary dilatation and increased permeability of the capillaries with the outpouring of excessive amounts of fluid. Therapy is directed toward the primary vasoconstriction. The course of treatment, as advised by Atkinson, is begun with the intravenous administration of 25 mg. of nicotinic acid, gradually increasing the dose for therapeutic effect if well tolerated. After the initial alleviation of symptoms, nicotinic acid in the dosage of 50 mg. is to be given by intramuscular injection every other day. Upon the patient's further improvement, the treatment is continued by the oral administration of niacin, 50 to 100 mg. daily.

Hallpike [29] attributes the beneficial effect of both histamine and nicotinic acid to their vasodilator action, which brings about an increase of the circulatory rate of the labyrinth. He considers the theory of histamine sensitivity as unsound from the standpoint of theoretic immunology. Ménière's disease does not occur in the young, and it most often attacks individuals who have no other manifestations of allergy. The fact that in some cases Ménière's disease runs its course in one ear and then begins to attack the other ear cannot be explained by an allergic hypothesis. As to the theory of desensitization to histamine, its rationale is to be questioned. Histamine, being a hapten, does not stimulate the production of antibodies. In the Report to the Council on Pharmacy and Chemistry of the American Medical Association,[30] Feinberg's review indicates that there is no conclusive evidence for the assumption that any degree of tolerance to histamine may be established by repeated injections.

The histamine-nicotinic acid treatment of Ménière's disease has found great favor in England. Clinical reports in support of this procedure were presented to the Royal Society of Medicine by Kodicek, Taylor, Bateman, Macleod and Hall.[31] At St. Thomas' Hospital in London, 53 Ménière cases were treated by this method. In 60 per cent, complete freedom from vertiginous attacks ensued, while another 38 per cent obtained some relief. Improvement in hearing, to the extent of 10 decibels occurred in 19 per cent. Tinnitus was ameliorated in 23 per cent, and some improvement took place in another 42 per cent.

Glass [32] reported phenomenal results from an accidental overdose of histamine given subcutaneously. Owing to an error, a batch of histamine was made up to the dilution of 1:10 instead of 1:10,000. Two patients received subcutaneous injections of 0.79 gm. instead of 1 mg. Both dropped completely unconscious, but recovered. Complete freedom from vertiginous attacks has been enjoyed by these patients ever since. Both regained their hearing, having been profoundly deaf before. In one case the normal hearing was maintained for six months, and in the other, for one month.

Sheldon and Horton [33] succeeded repeatedly in aborting Ménière attacks by the intravenous administration of histamine diphosphate, 2.75 mg. in 250 c.c. of saline, by the drip method.

Williams and associates [12] administered histamine intravenously daily, for a period of four weeks, to 32 individuals who were diagnosed as having endolymphatic hydrops without vertigo. Good results were obtained in 11 patients, who became free of tinnitus and whose hearing was restored to a conversational level or better. Repeat audiograms showed an improvement of 25 to 45 decibels.

"Histamine is a powerful physiologic agent for the fine adjustment of the circulation to varying local metabolic demands," says Dale.[34] In acute ischemia of the brain due to thrombosis, embolism and vascular insufficiency, the intravenous administration of histamine brought about improvement in 20 of 25 patients, according to Furmanski.[35] From a review of the literature on multiple sclerosis, Schumacher [36] finds that histamine is given to produce vasodilation rather than "desensitization." In Ménière's disease, the amelioration obtained from the subcutaneous injections of gradually increasing doses of histamine may be ascribed to vasodilation or to a "special form" of desensitization. However, the speedy and phenomenal effects that result from the intravenous administration of comparatively large quantities of histamine suggest an adjustment of the disturbed circulation of the inner ear.

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MÉNIÈRE'S SYNDROME AS A PREMONITORY SYMPTOM OF CEREBROSPINAL VASCULAR OCCLUSION: A REPORT OF TWO CASES *

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RECENTLY two cases have been seen in which the initial illness was indistinguishable from Ménière's syndrome but in which the final disease was an occlusion of the posterior inferior cerebellar artery. In one case a Ménière's syndrome was present for six days and in the other for two weeks before the arterial occlusion. One patient eventually recovered completely, whereas the second died.

Most authors [2, 8] feel that the diagnosis of Ménière's syndrome is relatively easy, but difficulty occasionally arises because there is no unanimity of opinion as to what actually constitutes Ménière's syndrome. The problem is further clouded by the obscure and evasive etiology. By far the most reasonable definition of Ménière's syndrome is that given by Dr. John R. Lindsay in a discussion before the Chicago Laryngological and Otological Society on January 3, 1944.[1] He stated, "The term 'Ménière's syndrome' has been used in connection with a group of diseases with paroxysmal vertigo, tinnitus and deafness which could not be explained on the basis of inflammatory disease, tumor or trauma." In other words, Dr. Lindsay prefers to make a diagnosis of Ménière's syndrome after the exclusion of other diseases. In addition to the time-honored triad of vertigo, tinnitus and deafness constituting Ménière's syndrome, other authors have added nausea and vomiting,[2] symptoms of peripheral vascular collapse,[2, 6] nystagmus,[2, 5, 4] headache,[5] hyperacusis,[8] transitory loss of vision without loss of consciousness,[7] transitory diplopia [6] and loss of consciousness.[6] Even though a diagnosis may be based on the three primary symptoms, further difficulty arises, as Horton [8] points out, because in many cases the three do not occur simultaneously. Confronted with this confusion, perhaps Dr. Lindsay's previously quoted view [1]—that Ménière's syndrome should be a diagnosis of exclusion—seems the wisest. This view is further substantiated by the presentation of these two cases.

On the other hand, an occlusion of the posterior inferior cerebellar artery, also known as Wallenberg's syndrome (1895), has a distinct, unmistakable clinical and pathologic picture. Briefly described, the posterior inferior cerebellar artery is a branch of the vertebral artery which supplies the inferior surface of the cerebellum, the ventral portion of the inferior cere-

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bellar peduncle, numerous structures of the medulla oblongata, and a portion of the choroid plexus of the fourth ventricle. The acute phase of this syndrome is characterized by the sudden onset of intense vertigo, nausea, vomiting, hiccough, aphonia, weakness and perspiration. One author [5] states that pain in the upper part of the face is a common finding. Although the blood supply to an extremely vital part of the brain is compromised, there is usually no loss of consciousness or sudden death. These acute symptoms usher in the following neurologic syndrome. On the homolateral side of the body there are analgesia of the face, anhidrosis, miosis, enophthalmos, ptosis, coarse ataxia and, of variable occurrence, vocal cord paralysis, palatal paralysis and paralysis of the tongue. On the contralateral side there are analgesia of the body and, occasionally, a hemiparesis. There are usually dysphagia, nystagmus and hypotonia.

This syndrome occurs most often in males between 50 and 60 years of age and is usually secondary to cerebral arteriosclerosis. The prognosis is usually good; in fact, as stated by Alpers,[3] the patient may weather an incomplete occlusion of the artery and remain ambulatory, or be forced to bed only by the severe vertigo. According to Goodhart and Davison,[9] this syndrome is seen infrequently, occurring only five times in their series of over 300 cerebral vascular accidents. Most authors feel that an occlusion of the posterior inferior cerebellar artery and an occlusion of the vertebral artery cannot be differentiated clinically.

Case Reports

Case 1. A 67 year old retired barber was admitted to the hospital on July 21, 1950, with the complaints of dizziness, headache, nausea and vomiting of three days' duration. The patient had been previously treated in the hospital from June 13, 1950, to July 8, 1950, for essential hypertension, hypertensive and arteriosclerotic heart disease, duodenal ulcer and cholelithiasis. He had been discharged on an ulcer diet without antacids.

The patient had been feeling quite well until three days before admission, when he was awakened from sleep by severe vertigo. This was followed by the appearance of a right suboccipital headache, nausea and vomiting. The vertigo was described as rotational, in a clockwise direction. Since onset, the vertigo had been severe and constant, and frequently accompanied by nausea and vomiting. Only partial relief could be obtained by lying still. For a period of several years the patient had noted a moderate deafness of his right ear. No tinnitus was recalled.

The essential physical findings on admission were as follows: Temperature, 97.8° F.; pulse, 88; respirations, 18; blood pressure, 198 mm. Hg systolic and 110 mm. diastolic. The patient's general appearance was that of an alert, elderly white man who was obviously dehydrated and ill. The eye examination revealed a bilateral horizontal sustained nystagmus, with the quick component toward the direction of gaze. The nystagmus was more prominent toward the right. Funduscopic examination revealed a grade three retinal arteriosclerosis and a grade two retinal artery constriction. There were no hemorrhages, exudates or papilledema noted. The external auditory canals were blocked by hard wax, and there was moderate deafness to the tuning fork on the right. The lungs were clear. Examination of the heart revealed the left border of cardiac dullness at 11.0 cm. in the fifth intercostal space. The rhythm was grossly irregular. There was a grade three apical systolic murmur.

The second aortic sound was exaggerated and increased in intensity over the pulmonic second sound. The abdominal and rectal examinations were normal. Neurologic examination revealed only those changes described under the eye and ear examinations, and an ataxia when walking was attempted. The vertigo could be exaggerated by lateral gaze to either side.

Laboratory examinations were as follows: hemoglobin, 15.6 gm.; red blood count, 5,250,000; white blood count, 16,200, with a normal differential. Urinalysis showed a specific gravity of 1.016, pH of 7.5, 20 mg. of albumin, no sugar, a few leukocytes and epithelial cells, an occasional hyaline cast and no red blood cells. Blood chemistry revealed a blood urea nitrogen of 14 mg. per cent; chlorides, 637 mg. per cent (as NaCl), and a blood carbon dioxide combining power of 65.8 vol. per cent. X-ray of the skull was normal. X-ray of the mastoid regions showed marked sclerosis of both mastoids. X-ray of the chest revealed moderate cardiac enlargement.

The patient was seen in consultation by Dr. A. B. Combs, of the Ear, Nose and Throat Department, who reported that both tympanic membranes showed scarring, retraction and calcium deposits. There was an old healed perforation of the right drum. No caloric test was performed.

During the first two hospital days the patient rested comfortably on conservative management of mild sedation and a low salt diet. Early on the morning of his third hospital day he was found by the nurse in an unconscious state. He had been incontinent of feces and urine. The temperature had suddenly risen to 104.6° F. rectally. The pulse was 88 and grossly irregular. The respirations were 32 per minute and of the Cheyne-Stokes type. Neurologic changes at this time were anisocoria, with the right pupil smaller than the left, and diminished deep reflexes in both legs. A lumbar puncture revealed an initial pressure of 260 mm. of spinal fluid. Approximately 6 c.c. of clear, watery spinal fluid were removed. Analysis showed 34 mg. per cent of protein; no cells were identified. The spinal fluid culture was negative.

Over a period of two weeks the patient very slowly regained consciousness but remained quite lethargic and listless. During this interval definite neurologic changes evolved. On the right side of the body there were miosis, enophthalmos, ptosis of the eyelid, paralysis of the palate and pharynx, and hypalgesia of the face. Over the left side of the body there was hypalgesia to pinprick. The voice had become quite hoarse, and consultation with Dr. Combs revealed a right recurrent laryngeal nerve paralysis. The nystagmus and vertigo had completely disappeared. There was no evidence of ataxia.

The patient was discharged on his twenty-sixth hospital day. Unfortunately, there has been no opportunity to reëxamine this patient since his discharge. Word from relatives, however, reveals that he has continued to improve, to a point where he walks without aid and no hoarseness is evident.

Case 2. A 59 year old white housewife was admitted to the hospital on September 18, 1950, because of dizziness, nausea and vomiting of two weeks' duration.

Since 1943 the patient had had diabetes mellitus, which was of a mild degree and easily controlled with diet and small doses of protamine zinc insulin. The patient had been observed on numerous occasions over a period of seven years for diabetic regulation and treatment of diabetic neuropathy in both legs. On several occasions rather large amounts of albuminuria were present, without any significant change in the formed elements.

For two weeks prior to her hospital admission the patient had complained of a more or less constant vertigo, which in the past few days had kept her bedridden. During the two days before admission there had been considerable nausea, associated on two occasions with vomiting. She complained also of abdominal bloating and anorexia. On direct questioning she stated that there had been a "humming" noise in her right ear, but was unable to state its duration. She had not noted any change in her hearing.

Physical examination on admission revealed a rather obese woman in no obvious distress. The blood pressure was 148 mm. Hg systolic and 98 mm. diastolic. The temperature was 98° F., the pulse 74 and the respirations 16. Examination of the skin, cardiorespiratory system and abdomen was not unusual. A neurologic examination revealed only bilateral horizontal sustained nystagmus with lateral gaze.

Laboratory studies on admission revealed a normal blood count. Urinalysis showed a specific gravity of 1.023, 3 plus glycosuria, no acetone, no diacetic acid, and 250 mg. per cent of albumin. Microscopic examination revealed 15 to 20 white blood cells and a rare red blood cell in a high power field of a spun specimen. Blood sugar on admission was 260 mg. per cent.

On her second hospital day, consultation with Dr. A. B. Combs, of the Ear, Nose and Throat Department, revealed by audiogram tests a mild hearing impairment of the right ear. Examination of the nose, ears and throat was negative.

During the first two hospital days the patient was treated with a low salt diet, ammonium chloride and regulation of her diabetes, without much change in her clinical condition. The patient continued to complain of dizziness, but there was no further vomiting.

On the evening of her third hospital day the nurse discovered the patient in a somewhat stuporous condition, sweating profusely and complaining of difficulty in swallowing and numbness in her left arm. Examination at the time revealed a pale, apathetic woman. The blood pressure was 180 mm. Hg systolic and 100 mm. diastolic; pulse, 108; respirations, 22; temperature, 98.2° F. There was profuse sweating over the left half of the face, while the right side remained dry and warm. There was ptosis of the right eyelid, and the right pupil was smaller than the left. The bilateral horizontal nystagmus remained as before. There was hypalgesia over the right side of her face and over the left arm. Sensory changes over the left leg were equivocal. There was a complete paralysis of the right half of the palate. Her speech had become muffled and less distinct. All the deep reflexes were active and equal. The abdominal reflexes were absent. No motor weakness was discernible. The Babinski reflexes were absent.

A urine test at the time showed a 3 plus glycosuria. In spite of this finding, the patient was given 50 c.c. of 50 per cent glucose intravenously, without any change in her clinical condition. Following this, the patient gradually became more lethargic, vomited several times, and died quietly about eight hours later.

An autopsy performed three hours later by Dr. M. A. Spyker showed grossly a complete thrombotic occlusion of the right vertebral artery which extended into and blocked the right posterior inferior cerebellar artery. Microscopic section through the medulla showed numerous perivascular hemorrhages on the right. The right vertebral artery showed severe ulcerative atherosclerosis with an organized thrombus.

Discussion

Although vertigo is considered one of the common and early symptoms of an occlusion of the posterior inferior cerebellar artery, the final diagnosis in these two cases was obscured by the fact that the vertigo had existed so long before the other signs and symptoms made their appearance. Before the onset of the neurologic syndrome a diagnosis of Ménière's syndrome was most likely in each case. In case 1, the patient presented only vertigo, nausea, vomiting and nystagmus, and diminished hearing was revealed by the audiogram. In case 2, the patient presented only vertigo, nausea and vomiting, and complained of a humming noise in her head.

A clinical and pathologic relationship between these two syndromes wherein confusion might exist is not clear-cut, and yet there is some common ground. The symptoms of vertigo, nausea and vomiting are common to each, and nystagmus is a frequent sign in both. Although of doubtful importance, headache has been described in each disease. An anatomic relationship exists in that the posterior inferior cerebellar artery supplies the vestibular nuclei and, according to Goodhart and Davison [9] and Baumoel and Friedman,[10] also supplies the cochlear nuclei so that impairment of hearing may be encountered.

There is very little reference in the literature of the past 25 years that brings out any relationship between these two entities. An occlusion of the posterior inferior cerebellar artery is rarely mentioned in any differential diagnosis of Ménière's disease or as one of the causes of vertigo. Baumoel and Friedman [10] present three cases of an occlusion of the posterior inferior cerebellar artery, and in their description of the clinical picture point out that the onset may be indistinguishable from Ménière's syndrome. According to them, two of the most important differential features are nystagmus and vocal cord paralysis. It is hard to believe that nystagmus is a reliable differential feature when most authors describe it as commonly occurring in both diseases. Lawson,[11] in discussing vertigo, presents a case very similar to those presented here. He says, "An interesting combination of nystagmus with recurrent laryngeal paralysis on the side of the nystagmus may be observed in a patient who has been treated for gastric disturbance because of the central vagus involvement. This combination is observed in acute disorders of the *arteria cerebellaris inferior posterior*, particularly with emboli or hemorrhage, encephalitis of the medulla, or in syringobulbia which is slow in onset and has a nystagmus most marked on the diseased side."

In view of the foregoing discussion, it seems logical to make Ménière's syndrome a diagnosis by exclusion. When presented with a patient with Ménière-like symptoms, one should be constantly alert to the appearance of other symptoms which might point to a more serious underlying disease. As illustrated here, one should watch carefully for the appearance of vocal cord, tongue and soft palate paralysis, Horner's syndrome and sensory changes in an elderly person with Ménière's syndrome. One should keep in mind that a Ménière-like syndrome also appears in association with acoustic nerve tumors, vascular aneurysms in the cerebellopontine region,[12] head injuries, inflammatory diseases of the labyrinth, motion sickness, toxic and infectious diseases, and cerebellopontine angle tumors.

Conclusion

Two cases are presented in which the initial clinical picture was indistinguishable from Ménière's syndrome but in which further developments proved the presence of an occlusion of the posterior inferior cerebellar artery.

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THE TREATMENT OF ANGINA PECTORIS WITH KHELLIN *

Part I

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The potent vasodilator action of khellin,† officially named visammin,[1] has been demonstrated in many pharmacologic laboratories by means of the heart-lung preparation and other technics during the past two decades. Among the earlier studies were those carried out by Fahmy,[2] Samaan [3] and Spaeth and Gruber,[4] while more recently Anrep, Barsoum and Kenawy [5, 6, 7] have proved that khellin has a more powerful action than many of the coronary vasodilators commonly employed. Toxicity studies in animals have not been numerous, but Samaan [3] found that the lethal dose in toads and rabbits was many times greater than the therapeutic dose, and the authors [8] demonstrated no pathology in the hearts, livers and kidneys of rabbits that received the drug intravenously every day for one month.

Rather comprehensive clinical studies of khellin in angina pectoris were also made by Anrep, Kenawy and Barsoum,[9, 10] who reported that khellin controlled the anginal pain without producing unpleasant reactions even when given in large doses of the order of 300 mg. daily. They stated that a daily maintenance dose of 50 to 100 mg., or even more, could be given for many months or even years without any untoward effects.[11] This contention that the drug produced no important untoward reactions was not confirmed by our experience. When we first gave khellin to a group of four patients in 1949, in divided doses of 300 mg.‡ daily, all developed severe nausea within a few days and use of the drug had to be discontinued. We therefore determined to administer a preparation allowing smaller doses of the drug to a larger group of patients with the anginal syndrome in order to evaluate the clinical response, and to ascertain the number, type and severity of reactions. Our study was based upon subjective criteria because it was known that other studies employing objective criteria, such as changes in the exercise tolerance test and in the ballistocardiogram, were being done.[12, 13]

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† The khellin used in this study was in the form of 20 mg. coated tablets supplied by the National Drug Co., Philadelphia, Pa.
‡ 100 mg. capsules of khellin supplied by the Warren-Teed Products Co., Columbus, Ohio.

Method

Forty-two patients with the anginal syndrome due to arteriosclerotic heart disease were selected to receive khellin orally and/or parenterally. The diagnoses were substantiated by careful history and complete cardiac evaluation, and many of the patients had been under observation and treatment with other drugs for several years. The group was comprised of 21 males, 12 of whom had old myocardial infarctions, and 21 females, four of whom had old myocardial infarctions. The patients ranged in age from 37 to 83 years, and the duration of the angina was from two days to 25 years, with an average of five years. Each patient was instructed to record the number and severity of anginal attacks and the number of nitroglycerin tablets used every day. All patients (except a few who were dangerously ill) were observed during a control period wherein they received no vasodilators at all. They were then started on khellin and observed for varying periods of time up to one year.

In some patients, therapy was instituted by having them take 100 mg. daily for several days and then dropping to a maintenance dose; but in the majority of cases the patient received one 20 mg. tablet a day for the first week and two tablets a day for the second week, and the dose was thereafter increased at weekly intervals by one tablet a day until a therapeutic response or a reaction occurred. In the event that the patient suffered undesirable side effects, the dose was decreased in an attempt to arrive at a nontoxic but therapeutically effective dose for that individual. When the therapeutic dose exceeded the toxic dose for a given patient, the khellin was usually discontinued at the insistence of the patient, but some patients continued to take the drug in spite of reactions.

A parenteral preparation of a suspension containing 50 mg. of khellin per cubic centimeter was employed both as a means of "rapid khellinization," wherein the patient received 50 to 100 mg. intramuscularly per day for three or more days, and as a "booster shot" of 50 to 100 mg., given once a week concomitantly with the oral medication. The former method was also employed in several cases of acute coronary occlusion not included in this series.

The khellin was administered continuously in most cases, intermittently in others, and some patients received other coronary vasodilators, such as erythrol tetranitrate, either alternately or simultaneously with the khellin. The clinical response to khellin was classified as favorable if the frequency and/or the severity of the anginal pains were diminished, as unfavorable if the reverse occurred, and as unchanged. All patients were examined at intervals of one week or less, and had periodic electrocardiograms and orthodiagrams. A few had ballistocardiograms, but not enough for us to form any opinion from the data.

Results

Reactions: These were purposely listed first because of the marked impression they made upon us and upon the patients. Of the 42 cases, 26 patients (or 62 per cent) developed one or more undesirable reactions. Nausea was by far the most common offensive symptom, occurring in 23 cases and accompanied by vomiting in six of these. There was one case of marked anorexia, one of epigastric pain, one of central nervous system stimulation with insomnia, one of tachycardia, and three of the male patients complained of a "hot feeling on top of the head."

Of the 26 cases with reactions, 12 patients had such severe symptoms that it was necessary to discontinue the drug. The other 14 patients either experienced relief from the undesirable symptoms when the dosage was decreased or were willing to endure minor discomfort as long as there was improvement in the anginal pain. Thus, 71 per cent of the total series were able to continue the khellin therapy for an average of six months.

Various methods were used in an attempt to diminish the number and severity of the side effects. The daily amount was given in divided doses; the medication was given before, during, after and between meals; some patients were instructed to lie down after taking it; some were given phenobarbital with it, and it was given with and without other vasodilators; but as far as we could tell, none of these measures was of any particular value in modifying the side effects.

The nausea may have been partially due to gastrointestinal irritation, but at least part of it was of central origin, as some patients became nauseated while receiving only the intramuscular preparation.

Clinical Response: Thirty of the 42 patients (or 71 per cent) experienced a decrease in the number and/or severity of the anginal pains, and therefore obtained a favorable response. This figure, of course, includes many who had reactions, some of whom were forced to discontinue the drug. Three patients (or 7 per cent) showed an unfavorable response, with increased pain, and six patients (or 15 per cent) were unchanged. The remaining 7 per cent consisted of three patients who died during the course of treatment, two from acute myocardial infarctions and one from an unrelated condition. These three all experienced relief from anginal pain in varying degrees prior to their deaths.

Of those who had old myocardial infarctions, a favorable response was shown by eight patients (or 50 per cent), a figure considerably below that for the entire series.

The group that showed improvement was about equally divided between male and female patients. The clinical response was apparently not related to the age of the patient or to the duration of the anginal syndrome. Some patients reported an improvement in their pain following a periodic intramuscular injection, although they were already on the maximal amount of

khellin that could be tolerated by the oral route, which indicates that they could not tolerate an effective therapeutic dose by mouth. One patient in the series who had bronchial asthma reported some improvement in his asthmatic condition along with relief from the anginal pain.

Some attempt was made to compare the efficacy of khellin with that of erythrol tetranitrate, but only an impression could be gained; namely, that in some cases one was superior to the other, and in others the combined use produced better results than either one alone. In five cases the response to khellin could be described as dramatic: the khellin quickly abolished their pain where other medication had failed.

Not included in this series were several cases of myocardial infarction which seemed to derive considerable benefit from intramuscular injections of 50 to 200 mg. of khellin daily during the acute phase. However, in acute myocardial infarction this drug, like others, is extremely difficult to evaluate.

A few patients with pain in more than one location were noted to experience relief from pain in one location but not in the other. One man noted that his chest pain was abolished but that the pain in his left arm recurred. This could not be explained, except, perhaps, on the basis that part of his pain was due to actual ischemia of the myocardium, and that the other element of pain was due to a secondary neuritis.

There was noted a wide individual variation in the amount of khellin necessary to produce a clinical response, also in the amount that would produce unfavorable reactions. The highest dose we were able to maintain for any length of time was 80 mg. per day. Some patients were able to tolerate only 10 mg. per day, and others were apparently able to tolerate none at all. Two patients taking 10 mg. daily still experienced pain but reported that the intensity of the pain was greatly reduced.

The average maintenance dose in those patients who had minor or no reactions and were able to continue the drug over a period of months was 40 mg. daily. It was felt that this was far below the effective therapeutic dose in many cases.

Discussion

In regard to the clinical response of patients with the anginal syndrome to khellin, our results showing 71 per cent favorable responses are in accord with most others thus far reported. Anrep, Kenawy and Barsoum [11] reported improvement in 140 of 250 patients. Rosenman, Fishman, Kaplan, Levin and Katz [14] found a marked reduction in the number of attacks in 11 of 14 cases of angina. Osher and Katz [15] reported improvement in 16 of 19 cases. Ayad,[16] with a series of 23 patients, obtained good results in 19 of them. Scott and co-workers [12] studied a group of 20 patients and observed a significant reduction in the number of anginal attacks in only four, but an additional 11 stated that their pains were less severe. The only completely negative results reported were those of Greiner and Gold,[17] who found khellin to be no better than a placebo.

Concerning untoward reactions, our experience, along with that of most other investigators in this country, is distinctly at variance with that of the Egyptian group. Anrep, Kenawy and Barsoum [11] barely mention side effects, and apparently did not encounter any severe enough to warrant cessation of therapy. However, Rosenman and co-workers [14] reported an incidence of 17 reactions in 43 cases, and Scott et al.[12] noted reactions in 17 of 20 cases, compared with our group of 42 patients, 26 of whom suffered undesirable side effects.

Various explanations have been advanced to account for the difference in the incidence of reactions to khellin in this country and in Egypt, but thus far they have been mostly speculative. Evidently the *Ammi visnaga* plant from which the khellin is derived is identical, since that used here is imported from the Mediterranean countries, although it is conceivable that there might be a regional variation within this area. It has been suggested that our methods of extraction may be different, and that we are obtaining an impure form of khellin. Another possibility is that the methods of essay may be different, and that we are using relatively larger doses. One fact appears to be certain: that the nausea is at least partly of central origin, since our patients developed nausea on intramuscular treatment alone as well as on oral treatment.

The difficulty in evaluating khellin as well as other forms of therapy in angina pectoris is of considerable magnitude, due to the large number of variables involved. It is well known that the severity of angina may be influenced by placebo therapy along with a multitude of environmental factors, and that the pain may undergo remissions and exacerbations for no apparent reason. It is also difficult to compare the various published series of cases because of the different methods and criteria of evaluating improvement. Some authors consider only a complete cessation of pain to be such, while others are satisfied with a decrease in the frequency or severity of the attacks. In the light of these facts, we feel that a study such as the present one is not subject to elaborate statistical analysis, but that it provides the basis for a definite clinical impression.

Our results with khellin and the results of others published thus far have given us no cause to change our preference for erythrol tetranitrate for the routine treatment of the anginal syndrome. We do feel that khellin is of value as a coronary vasodilator, however, especially in patients who fail to respond to the usual types of therapy; and that if the reactions could somehow be reduced to a reasonable number the drug would assume an important rôle in the treatment of the anginal syndrome. It should also prove to be useful in cases of acute myocardial infarction where the blood pressure is at a low level.

Summary

1. Forty-two patients with the anginal syndrome were treated with khellin (visammin) orally and/or intramuscularly for periods averaging

six months, and the clinical response was gauged by the number and severity of anginal attacks and the number of nitroglycerine tablets taken.

2. An incidence of 62 per cent reactions, mainly in the form of nausea and vomiting, was encountered, the reactions in 12 patients being severe enough to require cessation of therapy.

3. Thirty patients (or 71 per cent of the group) had a favorable response to the khellin, three patients (or 7 per cent) had an unfavorable response, six patients (or 15 per cent) were unchanged, and three patients, constituting the remaining 7 per cent, died before the study was completed after showing initial improvement.

4. Khellin is of value in the treatment of the anginal syndrome but will not replace the other vasodilators to any great extent unless a method of decreasing the incidence of side effects is discovered. The latter has reportedly been accomplished in Egypt, but certainly not in this country as yet.

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PARENTERAL ADMINISTRATION OF AMMIVIN (KHELLIN) IN THE TREATMENT OF CORONARY DISEASE *

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In recent years there has appeared on the market a drug named khellin, $C_{14}H_{12}O_5$, the active principle from a native Egyptian plant, *Ammi visnaga*, known since ancient times as an antispasmotic. This drug has been found to be a coronary vasodilator, with apparent potency about four times that of aminophylline. It is available for oral use in doses of 20 to 50 mg. in an enteric coated tablet. An abundant literature has appeared on the oral use of this drug.[1-5] However, many of these studies, while suggesting a good effect in the control of angina, report a high percentage of the patients as showing symptoms such as nausea, anorexia, vomiting and dizziness, making the persistent use of the drug difficult. Enteric-coating the tablet produced little if any change in tolerance, and reducing the frequency of dosage appeared to nullify whatever improvement the patient experienced from the use of the preparation. One gets the impression that the side effects are so undesirable that the patient has as much discomfort from the drug as from his cardiac complaints.

Barsoum and his co-workers [6] reported on the absorption of khellin and its estimation in blood and tissues. It was found to be rapidly absorbed from the stomach and intestines and long maintained in the circulation. The disappearance from the tissues and the lowering of the concentration in the blood were both extremely slow.

A search of the recent literature produces few references to parenteral khellin. Ayad [7] in 1948 used 100 mg. once or even twice a day for two weeks, then followed with oral medication. He reported that anginal attacks completely disappeared in 64 per cent, marked improvement occurred in 22 per cent and complete failure in 17 per cent. In five cases improvement was prompt; in most it appeared in five to 10 days. He reported no toxic effects. Anrep [2] in 1949 merely mentions its intramuscular use "in severe cases." Scott et al.[5] in 1951 commented briefly that "all patients receiving Visammin intramuscularly complained of burning pain at the site of injection." They studied electrocardiographic changes following single intramuscular doses of the drug and, in one case in five, found less marked RS-T segment depression after exercise than following control tests. Rosenman et al.[8] suggest that "in severe cases initial doses may be given intramuscularly." They apparently used 200 to 300 mg. every hour or two hours for an unknown period. One patient is said to have complained of local pain at the site of injection.

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Because undesirable side effects of oral preparations of khellin are frequent, it was decided to try intramuscular Ammivin,† a purified aqueous suspension of the active constituent in isotonic sodium chloride, containing 50 mg. of khellin per cubic centimeter. This was used in the treatment of a group of 18 ambulatory private patients with coronary disease, either with typical effort angina, with angina decubitus or with chronic coronary insufficiency. Most of these patients had either abnormal electrocardiograms consistent with a diagnosis of coronary disease, or a positive Master's step exercise test for coronary insufficiency where the resting electrocardiogram was negative. Two patients (cases 10 and 15), however, were thought initially to have coronary disease but had no supporting evidence, and in both of these khellin failed to produce any change in symptoms. In them, too, prolonged investigation revealed extracardiac causes for the chest symptoms. All of the patients had been under treatment with a variety of drugs, dietary regulation and restriction of activity of from one to 14 years before treatment was started. Patients were advised to continue using nitroglycerin when needed, but other drugs were omitted if possible.

Dosage levels were determined by trial and error. In a few, the intramuscular injections were given as often as every day (case 2), every two days (case 1), and every four days (case 8), in an effort to determine tolerance for the drug. The majority, however, after an initial dose of 1 c.c. intramuscularly, were given 2 c.c. once a week over a period of many months. Gastrointestinal disturbances at this dosage were entirely absent, but where the frequency of the injection was increased to every two to three days, nausea and vomiting often appeared, as with oral khellin (case 2). It was felt, therefore, that the gastrointestinal complaints depended on blood levels and were probably central in origin. It has been suggested by some investigators [8] that these side effects may be incidental, or due to the underlying cardiovascular disease. However, all patients in this series were free from such symptoms before the use of the drug by either mouth or injection, and in each case the symptoms very consistently followed the administration of the drug.

As is true with many drugs, there was considerable variation in the amount of local reaction to the injection. While six cases reported some tenderness or local heat and redness at the site, it was no more pronounced than that noted with mercurials or other standard injectables. In only one patient (case 6) was the first dose associated with so much edema, tenderness and pain that it was not repeated.

Use of vasodilator drugs has in general been disappointing. While oral aminophylline and similar preparations have been widely prescribed, it is questionable how much has been accomplished aside from the psychologic effect of taking a drug. Since angina pectoris, particularly the typical angina of effort, is a subjective symptom and frequently accompanied by no

† A National Drug Company product not yet released commercially.

objective changes in heart rate, blood pressure, heart sounds or cardiographic change, it is difficult to evaluate the actual severity of the pain or the definite effect of any medication. We must also keep in mind the fact that angina pectoris is a disease in which there are marked exacerbations and remissions occurring spontaneously even without medication. In this disease, too, many extracardiac causes may influence the frequency and severity of the pain, as, for example, unusual mental or emotional strain, intercurrent infection, gall-bladder disease, gastrointestinal disturbance, weight gain, coincidental hyperthyroidism and anemia.

Because of the difficulties inherent in judging the drug, the patient was instructed to keep a daily log of his reaction, using a modification of the "daily report card" suggested by Gold [10] for the evaluation of cardiac pain. He was given a dated card and was told that just before retiring he was to evaluate that day with a number from 1 to 4 as follows: (1) an unusually bad day, (2) a usual day, (3) an exceptionally good day, and (4) a day with no pain at all. This card, brought by the patient on his routine visits, enabled one at a glance to judge his condition over the previous weeks. It also reduced the chance of his magnifying recent discomfort or forgetting his previous state of health. Even with such a system, the figures themselves were not entirely consistent and the estimation of a "bad" or "good" day was apt to change over a period of time with the improvement or worsening of the patient.

As can be seen in table 1, the patients chosen had, in general, a long history or a progressive angina with an increased need for medication, and therefore what might be considered a control period before Ammivin was started. Several patients had voiced dissatisfaction with their progress and felt that nitroglycerin, while controlling the pain, failed to give them any sense of real improvement. Case 1 was such a patient. Oral khellin had been tried but found difficult to tolerate. He was therefore started on intramuscular injections of Ammivin, 100 mg. every two days for four doses and then a maintenance dose of one injection weekly. After starting the drug he had much less pain and was able to omit all Demerol and papaverine, previously used daily. In place of 8 to 10 nitroglycerin tablets, this drug was used at a maximum once or twice a week, and sometimes could be omitted entirely in spite of continuous increase in physical exertion. Case 3 received no khellin by mouth but was started immediately on 100 mg. of the drug intramuscularly every three days and then once a week. He needed no further nitroglycerin and, when last seen before leaving for Florida, he reported that he was able to wash his car and to walk a mile against a wind and still remain symptomless. Case 14 is very interesting. This man had had a severe grade of angina pectoris for at least six years, had been seen frequently and had required morphine for relief two to four times weekly because of the severity of the nocturnal attacks. When he was started on Ammivin he had a severe local reaction, with tenderness of

TABLE I

Coronary Heart Disease Treated with Parenteral Ammivin

Name Age Sex	Presenting Symptom and Duration	EKG Findings	Previous Medications	Date of Injections	Duration of Treatment	Dosage	Frequency of Dosage	Side Effects
FS #1 41 M	Angina of effort and angina decubitus following myocardial infarction—1 yr. ago	Old posterior myocardial infarction	Quinidine Papaverine Demerol Nitroglycerin	6–23–50 to 12– –50	6 mo.	2 c.c.	q. 2 days—4 doses; then q. 1 wk.	Nausea when drug pushed—none on weekly dosage
Comment: Need for nitroglycerin cut from 8 to 10 daily to 3 to 4 weekly. Other drugs omitted. Return of more angina with cold weather. Erythroltetranitrate b.i.d. begun—very infrequent angina. Patient working.								
FG #2 54 M	Angina of effort —14 yrs. Frequent angina decubitus	Pattern of left ventricular strain	Aminophylline Dilaudid Morphine Papaverine Nitroglycerin ETN Oral khellin Sedatives	7–26–50 to 9–15–50	2 mo.	½ c.c. to 2 c.c.	1 c.c. daily—8 days. Rest period 2 wks. Then q. 1 wk.	Nausea, vomiting, general muscular weakness and soreness starting after several days and continuing in spite of rest periods and reduction of dose
Comment: Unusually severe angina, using narcotics several times weekly and nitroglycerin 20 to 30 daily. Definite reduction in angina. Nitroglycerin cut to 4 to 5 daily. Fewer hypodermics. Treatment stopped because of severe side effects.								
AS #3 68 M	Precordial pain—5 yrs.	Coronary disease	Demerol Nitroglycerin	8–1–50 to 2–13–51	6 mo.	2 c.c.	q. 3 days—6 doses; then q. 1 wk.	None
Comment: Marked increase in activity. Rarely needs nitroglycerin. Patient's estimate of relief—80% better.								
VP #4 45 F	Angina of effort —5 yrs.	Negative at rest. EKG positive for coronary insufficiency after Master's Step Exercise Test	Aminophylline Oral khellin	10–3–50 to date	9 mo.	2 c.c.	q. 1 wk.—3 mo.; then q. 10 days	None
Comment: Question of continued employability as nurse. Rapid response to the injection, with almost complete eradication of angina on weekly doses; less well controlled on injections every 10 days.								

TABLE I—*Continued*

Name Age Sex	Presenting Symptom and Duration	EKG Findings	Previous Medications	Date of Injections	Duration of Treatment	Dosage	Frequency of Dosage	Side Effects
LS #5 49 M	Angina of effort —2 yrs.	Negative at rest. EKG positive for coronary insufficiency after Master's Step Exercise Test	Papaverine Demerol	10–6–50 to date	9 mo.	2 c.c.	q. 1 wk.	None
Comment: Severe anginal attacks 9 to 10 times daily interfering with work as auto mechanic. Good response to treatment. Nitroglycerin cut to 3 to 4 maximum, with occasional day without any pain. Working steadily.								
MB #6 65 F	Angina of effort —6 yrs.	Negative	Nitroglycerin Vasodilators Sedatives	10–10–50	One dose only	2 c.c.		Edema, redness and increased heat in arm and aching severe enough to prevent sleep. Required codeine, aspirin and ice cap
Comment: Patient refused further treatment.								
LM #7 66 M	Angina of effort —1 yr. Angina decubitus—many months	Coronary disease —possible old posterolateral myocardial infarction	ETN Nitroglycerin Aminophylline	10–20–50 to date	9 mo.	2 c.c.	q. 3 days—5 doses; q. 5 days —7 doses; then q. 1 wk.	None
Comment: Steady reduction in angina decubitus, which disappeared in 2 months. Nitroglycerin became effective. Improvement retained on reduced dose. Patient returned to work in October, 1950. Averages 0 to 2 nitroglycerin daily.								
MS #8 55 M	Angina of effort —8 yrs.; increasing angina decubitus	Coronary insufficiency	Vasodilators Nitroglycerin Papaverine Aminophylline	10–23–50 to 11–30–50	5 wks.	2 c.c.	q. 4 days—4 doses; then q. 1 wk.	None
Comment: Unremitting downward course previous to injections. Sudden death after five weeks of treatment. Patient had commented a few days previously, "This is the only thing that ever gave me any help."								

TABLE I—*Continued*

Name Age Sex	Presenting Symptom and Duration	EKG Findings	Previous Medications	Date of Injections	Duration of Treatment	Dosage	Frequency of Dosage	Side Effects
AB #9 59 M	Angina of effort following myocardial infarction—1 yr. ago.	Coronary artery disease with old anterior infarction	Nitroglycerin Alcohol	11–24–50 to 1– –51	6 wks.	2 c.c.	Twice a wk. for 2 wks.; then q. 1 wk.	Gastrointestinal discomfort when used twice a week. No reaction when taken once a week
Comment: Complete freedom from angina. Able to do considerable walking. No nitroglycerin required.								
SZ #10 47 F	Epigastric pain—1 yr.	Negative	Demerol Papaverine Aminophylline Estrogens Anti-spasmotics	11–29–50 to 3–2–51	4 mo.	2 c.c.	q. 1 wk.	None
Comment: No relief of symptoms. Final diagnosis—no coronary disease. Functional gastrointestinal symptoms.								
BS #11 71 F	Three severe attacks of coronary insufficiency and precordial pain not relieved by nitroglycerin—1 yr.	Probable coronary disease	Papaverine Phenobarbital Demerol Aminophylline suppository	12– –50 to date	7 mo.	2 c.c.	q. 1 wk.	None
Comment: Difficult to evaluate because of anxiety features. Less frequent and less severe precordial pain. Enough improvement for patient to want to continue treatment.								
LP #12 60 M	Angina of effort and angina decubitus—3 yrs.	Pattern of left ventricular strain	Nitroglycerin	3–29–51 to date	4 mo.	2 c.c.	Twice a week. Short trial with once weekly in May	None
Comment: Angina decubitus disappeared. Nitroglycerin decreased from 15 to 18 to about 3 daily. Reduced dosage coincided with recurrence of increased angina. Return to original dose with relief.								

TABLE I—*Continued*

Name Age Sex	Presenting Symptom and Duration	EKG Findings	Previous Medications	Date of Injections	Duration of Treatment	Dosage	Frequency of Dosage	Side Effects
SK #13 40 F	Angina of effort —2¼ yrs.	Pattern of left ventricular strain	Papaverine Phenobarbital Nitroglycerin	4–27–51 to date	3 mo.	2 c.c.	q. 1 wk.	None
Comment: Ten nitroglycerin before treatment. No nitroglycerin now necessary. Exercise tolerance much improved; walks without pain.								
EB #14 66 M	Angina of effort and angina decubitus—6 yrs.	Old anterior myocardial infarction	Nitroglycerin Morphine Aminophylline Phenobarbital Papaverine Atropine ETN Sedatives	5–7–51 to date	2½ mo.	1–2 c.c.	2 c.c. q. 4–5 days; reduction of dose and interval after 4 injections	Tenderness, local heat and redness of upper arm; nausea and vomiting
Comment: Narcotics omitted. Nitroglycerin formerly used up to 30 daily; recently 1 to 2 daily. Addition of Novocain and reduction of dosage abolished reactions.								
SA #15 63 F	Weakness; subscapular pain, precordial and arm pain with soreness and tenderness of left breast	Senile sinus arrhythmia. Flattened T wave in left precordial leads	Demerol Nitroglycerin ETN Vitamin B	5–9–51 to 6–7–51	1 mo.	2 c.c.	q. 5 days—2 wks.; then q. 1 wk.	None
Comment: Complete lack of response. Many emotional factors. Final diagnosis—pain probably noncardiac and due to arthritis of spine.								

TABLE 1—*Continued*

Name Age Sex	Presenting Symptom and Duration	EKG Findings	Previous Medications	Date of Injections	Duration of Treatment	Dosage	Frequency of Dosage	Side Effects
CD #16 61 F	Angina of effort —3 yrs.	Pattern of left ventricular strain	Atropine Phenobarbital Nitroglycerin ETN	5–26–51 to date	2 mo.	2 c.c.	q. 1 wk.	Slight soreness and heaviness of arm
Comment: Rheumatic aortic stenosis with functional coronary insufficiency. Cholelithiasis also present. Patient and daughter comment on "great improvement." Patient now has many days without pain.								
CQ #17 64 F	Angina pectoris —4 yrs. Angina decubitus—recent weeks	T wave changes suggestive of coronary artery disease	Digitalis Nitroglycerin Aminophylline Phenobarbital Papaverine Atropine	6–2–51 to date	2 mo.	2 c.c.	q. 1 wk.	Moderate local soreness at injection site—24 hours
Comment: Angina decubitus disappeared within two weeks. Anginal attacks were reduced from 4 to 5 severe attacks to less than 1 daily.								
TP #18 70 M	Angina of effort —3 yrs. Angina decubitus—1 mo.	Pattern of left ventricular strain	Demerol Nitroglycerin Papaverine Phenobarbital Potassium iodide	6–19–51 to date	6 wks.	2 c.c.	q. 1 wk.	Slight local soreness
Comment: Previous to treatment needed 10 to 12 nitroglycerin in spite of complete rest; now using 6 to 7 daily. Patient's comment, "This injection makes a new man of me for one day."								

the arm remaining for a week. The dose was given every four to five days and the anginal attacks became much less frequent. However, after the fifth injection he developed not only the local soreness but nausea, vomiting, anorexia and headache. Because of the good effect on his cardiac distress, Ammivin was not omitted but its dosage was reduced to 1 c.c., given only once a week and with the addition of 1 c.c. of Novocain. On this routine the patient tolerated the drug well for the next three doses. On raising the amount to 2 c.c. he again noted nausea and retching. However, he and his wife both stated that his angina had been cut down tremendously, and on resuming the weekly injection the drug was again tolerated. Case 2 was one of the first cases treated. Because of the severity and duration of his angina pectoris he was started with very heavy dosage of Ammivin, as noted in table 1. Within a few days he developed severe gastrointestinal symptoms lasting several days, relieved by omitting the drug and reappearing when the medication was resumed, even at lower dose. However, the patient felt sufficiently benefited in his angina to persist in the use of the injections for several months in spite of loss of weight and inability to eat. Eventually the reaction became so severe that it was necessary to cut Ammivin entirely. It is felt that in this case a much lower initial schedule would have been wiser.

Discussion

From the patients' standpoint, the drug was enthusiastically accepted, particularly by those who had been "through the mill," so to speak, in their search for therapeutic help and improvement. This improvement has thus far been maintained over longer periods of time than one would expect merely from the psychic effect of a new treatment. It is interesting, too, that in the two patients (cases 10 and 15) in whom coronary disease was somewhat doubtful or, if present, only partially the reason for the patient's distress, the drug failed to have any effect in relieving symptoms. Need for nitroglycerin in the average coronary case has been reduced; other drugs, and in particular the narcotics, are less often needed, and exercise tolerance is increased in some. In the author's opinion, one-third of these cases had excellent results in the control of a long-standing angina, and, with the exception of those unable to tolerate the drug or proved to have other sources for the pain, all other patients were at least moderately improved. Some patients have not as yet had the drug for a sufficient time truly to evaluate it, though the immediate effect is promising. Acute coronary insufficiency as evidenced by angina of decubitus is a particularly troublesome symptom, often lasting for many months in spite of vigorous treatment, and here too the impression is that it was more quickly controlled and eradicated with injectable Ammivin.

Local reactions to injectable Ammivin have been minor or absent in most cases, and when gastrointestinal effects were noted they were probably the result of improper dosage. It will be necessary to learn by future trial

how to use the drug most efficiently, especially in view of reported cumulative effect. In the early days of digitalis therapy, nausea, vomiting and purging were considered a necessary accompaniment of its therapeutic effect. With Ammivin, too, patients may need to be saturated with the drug and then maintained on smaller doses. Laboratory aid in the form of a test for the concentration of the drug in the blood stream would provide a more critical means of determining its effective therapeutic level.

In evaluating any new drug, two questions may be asked: (1) Is it effective in relieving symptoms? and (2) Does it alter favorably the natural course of the disease? In answering the first, it appears that intramuscular Ammivin shows promise and certainly warrants further trial. The results appear much more consistent than those obtained with oral preparations and, by proper dosage, the troublesome gastrointestinal reactions can be entirely avoided. As for the second question, long-term treatment of many patients will be needed to evaluate true increase in coronary blood flow and improvement in cardiac competence.

Summary

1. A series of 18 ambulatory patients, previously under observation for severe and recurrent precordial pain due to coronary disease, was treated over a period of months with parenteral khellin (Ammivin).

2. The drug was administered intramuscularly in varying amount and at varying intervals in an effort to obtain an optimal therapeutic effect without side effects.

3. Tabulation of case findings was made, and results were encouraging in that a majority of patients noticed less frequent and less severe attacks, with reduced need for auxiliary medication.

4. The drug deserves further trial and study in the treatment of angina.

Addendum

Since this manuscript was submitted, cardiograms following Master's step exercise have been repeated on patient VP (Case 4) and are now negative. This patient continues to take the injection once a week, uses no nitroglycerin for weeks at a time and is working full time as a general duty nurse.

Acknowledgment

The author wishes to express thanks to Dr. Gabriel Pickar for the data on cases 11, 12 and 13.

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THE TREATMENT OF ANGINA PECTORIS WITH PURE CRYSTALLINE KHELLIN *†

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Introduction

The use of khellin in the treatment of angina pectoris has been the subject of numerous reports.[1-5] The results have varied from those who reported 90 per cent improvement [1] to those who found it to be no better than a placebo.[4] Some possible causes for these discrepancies include spontaneous changes in the disease process, different methods of evaluating the results, and variations in the size of the dose of khellin used by the different workers.

In a previous report,[5] we found only four of 20 patients studied who showed a definite reduction in the number of their anginal attacks while receiving khellin. Moreover, a relatively high incidence of untoward side effects was encountered in the 20 patients. Many of these patients were unable to tolerate more than 40 mg. of khellin per day, which is believed to be an inadequate daily dose in most instances. The preparation used in that study was stated by the manufacturer § to consist of a mixture of 70 to 80 per cent khellin and 20 to 30 per cent visnagin, each tablet containing the equivalent of 40 mg. of active principle. Preparations of similar mixtures have been used in other reports.[3-6] It was believed that many of the patients in that study were not maintaining an adequate therapeutic level. It was suggested that impurities in the mixture might be responsible at least in part for some of the side reactions, and that the latter were not due entirely to khellin. A purified crystalline khellin preparation (approximately 99 per cent pure) which was made available to us seemed to offer promise of an answer to those questions.**

The present study was undertaken to determine if the purified crystalline khellin would cause undesirable side effects in dosage levels that were considered adequate. In addition, it was desired to learn whether, if such dosage could be achieved, there would be definite improvement in the anginal seizures.

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This study was aided in part by a grant from Lloyd Brothers, Inc., Cincinnati, Ohio.

† Khellin, 2 methyl 5, 8-dimethoxy-furano-chromone, is the presently accepted generic name of the Council on Pharmacy and Chemistry. This compound was previously designated as visammin.

‡ Trainee of the National Heart Institute.

§ Smith, Kline, and French Laboratories, Philadelphia, Pennsylvania.

** The khellin used in the present study was supplied as Khelloyd, a pure crystalline form of khellin, by Lloyd Brothers, Inc., Cincinnati, Ohio, through the courtesy of Dr. L. J. Klotz.

Methods and Materials

Fourteen patients with well-authenticated angina pectoris were selected for this study. The majority of these patients had been followed for several years in the Cardiac Clinic and the Cardiac Laboratory of the Cincinnati General Hospital. Their ages ranged from 47 to 79. Each patient kept a daily record of his pains on a small card made in the form of a calendar.[8, 9] He brought this card with him at each visit and the number of pains was transcribed on a master sheet in the form of a permanent record for each patient. Some patients were taking digitalis, and this was continued. The patients were permitted to take nitroglycerin tablets as needed.

The patients in this study can be divided into three groups, on the basis of the severity of their angina during the control period: three had what we can arbitrarily call mild angina (fewer than two pains per week); seven had moderate angina (between two and 10 pains per week); four had severe angina (over 10 pains per week).

All of the patients were observed for a control period of an average of four weeks prior to the administration of either crystalline khellin or placebo. Upon completion of the period of control observation, each patient was given either 50 mg. doses of crystalline khellin four times a day, or a placebo identical in size and color. This trial with either khellin or placebo was conducted for an average of four weeks. At the end of this period the preparations were changed, and those who had been receiving placebo were now given khellin, and vice versa. The physician who dispensed the tablets did not know their identity.

Exercise tolerance tests were carried out on each patient during the control period and at the end of each period of trial with khellin and placebo. The test required that the patient walk over two standard 9 inch steps with a small piece of ice in each hand.[8] He was required to perform a double Master test (twice the designated number of trips for his age and weight in three minutes), unless he developed pain or severe dyspnea. An electrocardiogram, including standard leads I, II and III, precordial leads V_3, V_4 and V_5, and augmented unipolar extremity leads aVL, aVR and aVF, was taken before and immediately following the exercise test. The test was considered positive if there developed an RS-T segment depression of 0.5 mm. or more in standard leads I and II, in aVL or aVF or in the precordial leads.[10] Change in direction of a T wave following exercise was also regarded as a positive test.

Results

Eight of the 14 patients studied experienced fewer pains while taking the purified crystalline khellin than during either the control period or while taking placebo (table 1). Five of these patients (J. D., W. Sch., E. C., M. P. and R. H.) had over 50 per cent reduction in the frequency of their anginal attacks.

When our patients are grouped according to the severity of their angina, it is found that the more severe the case the more striking the improvement. Three (M. O., M. M. and J. W.) of the four severe cases, four (J. D., W. Sch., E. P. and R. H.) of the seven moderate cases, and one (M. P.) of the three mild cases showed significant improvement while taking pure crystalline khellin.

Because our series of patients has been previously studied over a comparatively long period of time, and because of the relatively good correlation between the number of anginal attacks during the control period and the number during the period of placebo administration (table 1), it is felt that the significance of the results with khellin is increased.

TABLE I

Patients	Periods of Study					
	Control		Placebo		Khellin	
	Weeks	Average Attacks per Week	Weeks	Average Attacks per Week	Weeks	Average Attacks per Week
J. D.	4	8.3	5	9.1	4	0.24
M. O.	6	20.6	3½	22.5	5	13.8
M. M.	4	23.8	6	13.2	4	10.3
W. Sch.	6½	5.6	4	7	6	1.9
E. C.	3	8	6	6.1	4	1.8
M. P.	4	1.8	5	1.4	7	0
J. W.	7	10.4	3½	11.8	4	7
R. H.	4	2.8	5	0.6	4	0
G. S.	4	2.8	4	0.3	4	0.3
C. C.	3	6	4	1	5	1.2
A. H.	8	0.9	4	0.3	4	1.3
M. W.	4	2.8	4	2.8	4	2.2
N. G.	4	1	4	0	2½	0
J. M.	2	9	5	4.8	6	6.7

Six of the patients showed no significant decrease in the frequency of their pains while taking purified crystalline khellin (table 1).

Khellin requires a few days to reach a maximal therapeutic level in the body, and also requires several days or even weeks to be completely excreted after therapy is discontinued.[1, 4] With these facts in mind, we have also analyzed our data by omitting the first seven days of khellin therapy and also the first seven days of those periods of placebo administration which followed khellin therapy. Nine patients showed improvement while on khellin therapy, one more than the number obtained when the data were analyzed according to the first method (table 1). In addition, six of these nine showed over 50 per cent reduction in the frequency of their anginal attacks.

Fifty-one exercise tolerance tests were performed on the patients during this study. During the control period all of the patients had a positive test,

as manifested by the occurrence of anginal pain or the development of positive electrocardiographic changes, or both.

Exercise tests were performed on all patients following placebo administration, with the exception of one patient (J. M.), who could not exercise because he had developed cellulitis of his legs. None of the patients showed increased performance or reversal of electrocardiographic changes following placebo administration.

Exercise tests were done on all patients at the end of khellin therapy except for one (N. G.), who was hospitalized for a suspected myocardial infarction, as described later. Three of the patients tested showed improvement in their exercise tests following khellin therapy. One patient (R. H.), who had positive electrocardiographic changes following exercise during the control and placebo periods, had a negative test after khellin administration; however, there was no increase in the number of trips he was able to perform. One patient (C. C.) showed slightly less marked RS-T segment depressions in her electrocardiogram following exercise during the period of khellin therapy than she did during either the control or placebo periods. One patient (G. S.) was able to perform 36 trips following khellin therapy, as compared with 27 and 24 trips during the control period, and 30 during the placebo period; his electrocardiogram was positive after each test.

Side Effects and Dosage

Purified crystalline khellin therapy was initiated in the form of 50 mg. uncoated tablets four times daily. Three patients (G. S., M. M. and R. H.) tolerated the dose for the entire period of observation with absolutely no side effects (table 2).

The most common side effect observed was the appearance of nausea. The nausea, however, was readily controlled in most cases by reduction of dosage.

Seven patients (J. W., M. O., C. C., M. P., E. C., N. G. and J. M.) developed nausea on a dosage of 200 mg. per day. In two patients (J. W. and M. P.), the dose was reduced to 100 mg. with no recurrence of the nausea; in one patient (M. O.), the dose was reduced to 150 mg. per day and she had complete subsidence of her symptoms except for slight nausea on one day only. Patient J. M. had no recurrence of nausea on daily doses of 100 or 150 mg. A fifth patient (E. C.) stopped khellin for one week and then resumed her medication on a dose of 200 mg. daily with no recurrence of nausea. Patient C. C. stopped khellin for one week, then took 100 mg. a day for two weeks and then 200 mg. a day for a week with no recurrences of nausea. The seventh patient (N. G.), who will be referred to later, discontinued khellin on two occasions because of untoward effects. Other symptoms noted by these seven patients are listed in table 2.

One patient (J. D.), on the second day of khellin therapy (200 mg. per day), had marked urinary frequency and polyuria and generalized malaise.

TABLE II

Patient	Daily Dose of Khellin in mg.	Duration	Side Effects
J. D.	112 (average) (Range: 200–0)	29 days	Frequency, polyuria, generalized malaise noted on 200 mg. per day but not on 100 mg. per day.
M. O.	200 150	18 days 16 days	Nausea. Slight nausea on one day only.
M. M.	200	28 days	None.
W. Sch.	200 100 None 150	7 days 27 days 7 days 7 days	Diarrhea (but he had been troubled with this when not on khellin). Patient stopped khellin but diarrhea persisted.
E. C.	200 (took less than 200 2 days/wk.) None 200	21 days 7 days 7 days	Gaseous distention, epigastric pain periodically. Stopped because of nausea and epigastric pain. None (no recurrence of symptoms when dosage was resumed).
M. P.	200 100	6 days 33 days	Slight nausea, pyrosis. None.
J. W.	200 100	5 days 23 days	Nausea, anorexia, generalized malaise. None.
R. H.	200	28 days	None.
G. S.	200	28 days	None.
C. C.	200 None 100 200	14 days 7 days 14 days 7 days	Weakness, anorexia. Stopped because of nausea; vomited once. None. None.
A. H.	175 (average) (Range: 100–200)	28 days	Sour eructations with 200 mg. dose, none with 150 mg. dose.
M. W.	200	29 days	None.
N. G.	100 (average) (Range: 0–200)	17 days	Nausea, anorexia, pyrosis, "metallic" taste; patient stopped tablets twice because of nausea.
J. M.	200 150 100 150	10 days 5 days 6 days 21 days	Nausea. None. None. None.

He reduced his dose (omitting the tablets entirely on some days), so that he averaged approximately 100 mg. per day. On this dose there were no untoward effects. Another patient (A. H.) experienced sour eructations while on a daily dose of 200 mg., but had none when he reduced the dose to 150 mg. per day.

Patient W. Sch. experienced diarrhea while taking khellin, but this in all probability was not due to the drug; this patient had been troubled with diarrhea before the study began and experienced it also while taking placebo.

Discussion

Seven of the 11 patients with moderate or severe angina had a definite reduction in the frequency of their anginal pain while taking purified crystalline khellin (table 1). Two of these were maintained on a daily dose of 200 mg. throughout the period during which khellin was administered. The other five, after being on a daily dose of 200 mg. for from one to 18 days, required a reduction in their dose (because of side effects) to an average of 100 or 150 mg. per day.

Of the six patients showing no improvement, three had mild angina. Other workers [5] have pointed out the difficulty of evaluating the effect of any drug in patients suffering from infrequent anginal seizures. One patient (N. G.), after being on 200 mg. of khellin for four days, experienced an episode of severe dyspnea without pain. He was hospitalized for 17 days for observation and khellin was discontinued. Although a myocardial infarction was suspected clinically, he never developed any electrocardiographic changes. After discharge from the hospital he was again started on khellin, but he discontinued the tablets on two occasions because of nausea, anorexia and pyrosis.

Nine of the 14 patients in this series had one or more side effects (table 2) on a dose of 200 mg. per day. However, in all but the one case noted above, these side effects completely disappeared on reduction of the dose to 150 or 100 mg. per day. In two instances, by either temporarily reducing the dose or omitting it entirely for one week, the patient was then able to resume a daily dose of 200 mg. without side reactions.

The striking feature is that, in this series, all except one of the 14 patients were maintained on an average daily dose of purified crystalline khellin of 100 mg. or more throughout their period of khellin therapy. This is in contrast with our earlier study,[8] in which, when using a khellin mixture, seven of 20 patients studied could tolerate an average daily dose of only 17 to 60 mg. of active principle because of the occurrence of untoward side effects.

Of interest is the fact that even the patients who showed no improvement were maintained on average daily doses ranging between 100 and 200 mg. of purified crystalline khellin. This would seem to indicate that some patients will not improve despite an adequate therapeutic level of khellin. This is in accord with the statement that approximately 30 to 40 per cent of patients with angina pectoris do not respond to drug therapy.[6, 11, 12]

On the basis of this study, it appears that purified crystalline khellin causes fewer side effects in doses considered to be in the therapeutic range than does the khellin mixture. Some of the side effects of the latter are probably caused by impurities.

A suggested dosage schedule is to administer four 50 mg. tablets of purified crystalline khellin daily in divided doses. This should be main-

tained unless side effects occur, in which case the dose should be reduced to two or three tablets daily.

Based on the period of observation used, our studies indicate that dosage of pure crystalline khellin may be adjusted in many patients practically to eliminate untoward side effects while still remaining within what is generally considered to be the therapeutic range. We consider the minimal effective dosage to be 100 mg. or more per day.

Summary and Conclusions

1. Purified crystalline khellin was administered orally to 14 patients with angina pectoris.

2. These patients were observed during a control period and two subsequent periods of alternate placebo and khellin administration. These periods each averaged approximately four weeks.

3. Eight of the 14 patients experienced fewer anginal attacks while taking purified crystalline khellin than during either the control period or the period of placebo administration.

4. The purified crystalline khellin was started in a daily dose of 200 mg. in all patients.

5. Nine of the 14 patients experienced one or more untoward side effects while taking 200 mg. per day. In all but one of these patients the side effects could be controlled by temporarily discontinuing the khellin or by reducing the dose to 150 or 100 mg. per day.

6. Exercise tolerance tests were performed during the control period and upon completion of the period of placebo and khellin administration. Three patients showed improvement in their exercise tests following khellin therapy.

7. This study indicates that purified crystalline khellin produces fewer side effects than do khellin mixtures in doses considered to be in the therapeutic range.

Acknowledgment

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COMPARATIVE TESTS OF THYROID FUNCTION *

By George B. McAdams, *Hartford, Connecticut,* and William T. Salter, F.A.C.P., *New Haven, Connecticut*

In this report are included comparative studies on approximately 45 patients whose thyroid function was appraised by four laboratory tests, in addition to routine clinical observations. These laboratory tests were:

(1) Serum "hormonal" iodine (protein-precipitable), S.H.I.
(2) Basal metabolic rate, B.M.R.
(3) 24-hour uptake of radio-iodide, I^{131}.
(4) Thyroid secretory rate, T.S.R., which was determined by the turnover of radio-iodide in the gland, as described by Salter, de Visscher and McAdams.[1]

The chief objective was to validate laboratory means for distinguishing between hyperplasia and hyperfunction of the thyroid in the goitrous patient.

The patients studied comprised a wide range of individuals, from athyreotic and pituitary myxedema to severe primary hyperthyroidism (Graves' exophthalmic goiter). As shown in table 1, females predominated, but there was a considerable variation in age. The patients selected were *untreated,* for reasons which will appear later. Special care was taken to exclude the previous use of thiouracil congeners and of iodine-containing medication, including radio-opaque media used for x-ray diagnosis. Both ambulatory and hospitalized patients from the Hartford Hospital were included.

Methods

All patients received 100 microcuries of I^{131} orally, fasting. With the portable Tracerlab monitor model SU-4, direct contact readings were taken at several anatomic sites. These were (a) over the neck in the regions of the isthmus and over the two lobes; (b) over the manubrium, and (c) against the calf of the legs. The readings were repeated at intervals of one or two hours, four, eight and 24 hours after administration of the test dose. At the 24-hour period, the percentage uptake in the gland was determined with a "100 scaler," Tracerlab model SC-7, by taking five minute readings at 15 cm. above the neck of the recumbent patient directly over the isthmus. Such values were compared with the readings of a standard bottled solution containing 100 microcuries made up at the same time the

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patient was treated. Background readings (at the calf) were subtracted from the neck readings. Likewise, environmental background readings were subtracted from the standard readings before the percentage uptake was calculated. In connection with the contact neck readings, the background (calf) readings were not subtracted, inasmuch as in no case was this greater than 3 per cent of the neck readings. Indeed, in the hyperthyroid cases they were all less than 1 per cent. The basal metabolism tests were done in the referring doctor's offices or in the Hartford Hospital, some

TABLE I

(1) No.	(2) Patient	(3) Sex	(4) Age	(5) Hospital No. or Doctor	(6) S.H.I., mcgm. %	(7) B.M.R., % of Normal	(8) 24 Hr. Uptake I^{131}, % of Test Dose	(9) T.S.R., mg. L-thyroxine X2	(10) Estimated T.M.R. X2
				Hypothyroid					
1	Re	M	52	665–771	1.7			0.10	0.09
2	Pad	F	78	699–458	1.7		14.4	0.11	0.09
3	Ro	M	60	681–109	2.3	−14	10.0	0.11	0.11
4	Wh	M	38	Dr. E. Nichols	3.1			0.12	0.14
5	To	F	66	694–960	3.6	−9	17.3	0.11	0.16
6	Ke	F	23	Dr. Pyrtek	3.6	+3	23.6	0.29	0.16
7	Ri	F	49	OPD	3.7	−20	22.3	0.13	0.16(5)
8	Bl	M	31	Dr. Roh	3.7	+42	19.7	0.20	0.16(5)
9	deP	F	50	OPD	3.8	+19		0.17	0.17
10	St	M	63	694–214	3.8			0.17	0.17
11	Ha	F	73	Dr. J. Clancy	3.8	+40	10.7	0.10	0.17
12	Qu	M	48	OPD	3.8	−29	38.0	0.27	0.17
13	McP	F	46	OPD	3.9	−12		0.18	0.17
				Euthyroid					
14	Pro	F	55	Dr. S. Root	4.0		27.1	0.23	0.17(5)
15	Hu	F	53	692–664	4.1	+25	49.0	0.21	0.18
16	Pl	F	53	695–764	4.3	+13	19.9	0.19	0.20
17	Suf	F	46	OPD	4.5	+42	19.7	0.27	0.19(5)
18	To	F	35	OPD	4.6	+10	30.1	0.17	0.19(5)
19	Pra	F	37	Dr. Root	4.9	−1	40.0	0.19	0.21
20	Ha	F	40	Dr. Dushane	4.9	−8	31.2	0.28	0.21
21	Os	F	26	Dr. Prestley	5.3	+19	27.0	0.21	0.22(5)
22	Suru	F	70	675–737	5.3			0.33	0.22(5)
23	Lo	M	34	698–074	5.3	−9		0.19	0.22(5)
24	Suro	F	55	69–87–42	5.3		17.1	0.23	0.22(5)
25	Par	F	53	Dr. Prestley	5.4	+27	70.8	0.35	0.23
26	Mu	F	29	Dr. J. Carroll	5.4	+22	18.0	0.19	0.23
27	Pe	F	59	698–496	5.7	+78	17.2	0.17	0.24
28	No	M	43	690–125	5.9			0.15	0.25
29	DiN	F	32	665–801	5.9			0.14	0.25
30	Wi	F	22	69–87–80	6.2	+1	35.7	0.38	0.26
31	Lo	F	29	687–629	6.3	+40	32.0	0.19	0.26(5)
32	Sz	F	41	OPD	6.5	−10	28.0	0.23	0.27
33	Be	F	48	69–94–39	6.6	+33	17.2	0.18	0.27
34	Sa	M	63	Dr. Waltman	6.8		7.8	0.13	0.28
35	Sh	M	35	69–97–23	7.1	−14	16.5	0.23	0.29
36	St	F	64	692–130	7.7	+18	84.0		0.31(5)

TABLE I—*Continued*

(1) No.	(2) Patient	(3) Sex	(4) Age	(5) Hospital No. or Doctor	(6) S.H.I., mcgm. %	(7) B.M.R., % of Normal	(8) 24 Hr. Uptake I^{131}, % of Test Dose	(9) T.S.R., mg. L-thyroxine X2	(10) Estimated T.M.R. X2
				Hyperthyroid					
37	K1	F	40	Dr. Calef	9.9	+33	46.5	0.45	0.40
38	Gr	F	62	665-092	10.8	+5		0.38	0.43(5)
39	Si	F	50	Dr. Jenovese	11.2	+45	60.5	0.43	0.45(5)
40	Su	M	64	OPD	11.6	+75	64.2	0.39	0.46
41	Wa	F	38	Dr. Jenovese	14.2	+13	47.4	0.53	0.56
42	Se	F	27	Dr. Root	14.7	+47		0.64	0.58
43	Ch	F	39	689-000	14.8	+34	63.0	0.59	0.58(5)
Coefficient of correlation vs. estimated T.M.R. (Column 10)					1.00	0.44	0.58	0.87	
Probability value, *P*					<0.001	<0.01	<0.001	<0.001	

Column 6. Serum "hormonal" iodine (micrograms per cent).
Column 7. Basal metabolic rate (percentage of normal).
Column 8. 24-hour uptake of I^{131} (percentage of test dose).
Column 9. Thyroxine secretory rate (mg. L-thyroxine secreted by the thyroid gland per day per square meter of body surface).
Column 10. Estimated thyroxine metabolic turnover rate (mg. L-thyroxine consumed per day per square meter of body surface).
In columns 9 and 10 the physiological value has been doubled to equate it with the dosage of parenteral DL-thyroxine, now available for therapy.

in the out-patient department, some on the wards. Finally, the serum "hormonal" iodine determinations were performed according to the cold-acetone precipitation method of Salter and Johnson as modified by Salter and Rosenblum.[2]

CALCULATION OF THYROID SECRETORY RATE, T.S.R.

As outlined previously,[1] the radioactivity of the thyroid gland is determined by (a) hyperplasia of tissue, and (b) its functional activity. Hence, the *decline* in glandular radioactivity due to secretion of hormone must be integrated with the *increase* in pick-up due to trapping of iodide. When this correction is made, the distorting effect of hyperplasia largely disappears, and only the secretory rate is recorded. In particular, euthyroid cases with nontoxic goiter register as "normal function," whereas without suitable correction the value for pick-up is high.

The formula for the calculation follows:

$$\text{T.S.R.} = 0.07 + 0.378 \times P \times \text{antiln}\left(-\frac{\ln S}{10\,r}\right)$$

In this equation,

P = maximal up-take (in counts per minute per microcurie $\times 10^{-2}$) within the first eight hours.
S = the rate of uptake in the first six hours; and
r = ratio P/A, where
A = the final up-take at 24 hours (in C.P.M. per $\mu c \times 10^{-2}$).

T.S.R. is conveniently stated in terms of milligrams of L-thyroxine per square meter of body surface per day. The numerical coefficients shown in the equation are for the particular instrument employed, as described earlier.

Laboratory Findings

The collective data are shown in table 1 and in figures 1 to 5. The daily T.M.R. (thyroid metabolic turnover rate) was estimated from the serum analyses according to Salter, de Visscher, McAdams and Rosenblum [3] and included in table 1. For convenience, this T.M.R. was chosen as the chief parameter, against which all other findings were compared. For each test-series, given in a single column of table 1, the correlation with the T.M.R. was calculated as a coefficient by the method of Fisher.[4] Perfect correlation is indicated by a value of 1.0, and absolute lack of correlation by a value of 0. From the table it will be seen that the serum "hormonal" iodine (known as S.H.I or P.B.I.) shows nearly perfect correlation with the T.M.R. This feature follows naturally, as one is estimated from the other. Obviously, for present purposes, either value may be used as a "standard" parameter of reference.

Basal Metabolic Rate

The B.M.R. showed only moderate correlation, as indicated by a coefficient of 0.44, shown in column 7 of table 1. Figure 1 illustrates the scatter involved. Nevertheless, this value is high enough to indicate a definite diagnostic usefulness of the B.M.R. However, the test proved to be slightly worse than the 24-hour uptake of radio-iodide.

24-Hour Radio-iodide Uptake

The difficulty with the measurement of 24-hour uptake of radio-iodide is that it reflects anatomic hyperplasia as well as physiologic hyperfunction. Accordingly, the correlation with T.M.R. (thyroid metabolic turnover rate) is only 0.58. Figure 2, indeed, shows about the same scattering as figure 1.

Thyroid Secretory Rate

The thyroid secretory rate, as calculated by Salter, de Visscher and McAdams,[1] is based upon a series of readings. It recognizes the rapid release of hormone by the hyperfunctioning gland, while correcting for

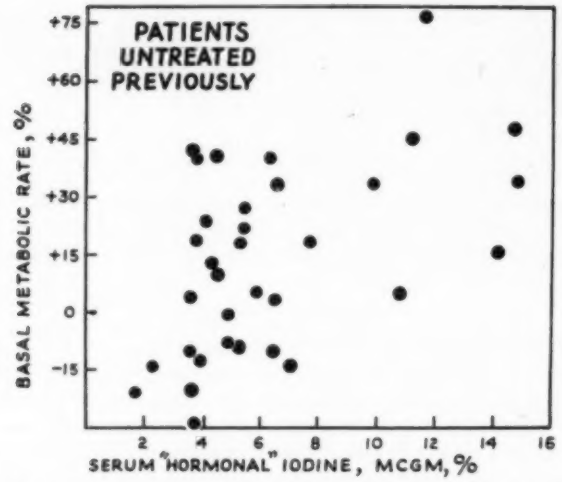

FIG. 1. Basal metabolic rate compared with serum "hormonal" iodine in 33 patients.

hyperplasia. As shown in table 1 (column 9), the coefficient of correlation is high, i.e., 0.87. Moreover, figure 3 shows less scattering than the earlier graphs. In short, T.S.R. (measured over the thyroid gland) correlates well with T.M.R. (measured in the blood), *if the patient is in a steady physiologic state.*

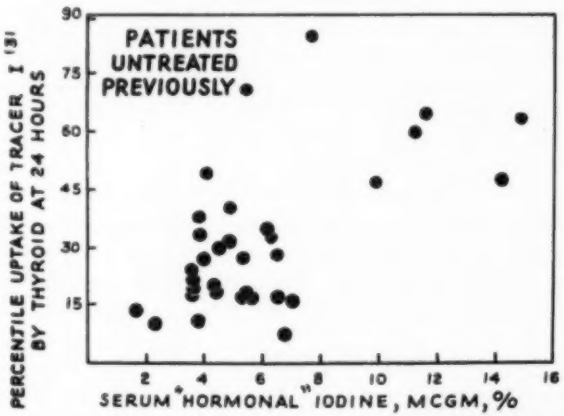

FIG. 2. Twenty-four hour percentile uptake of radio-iodide compared with serum "hormonal" iodine in 32 patients.

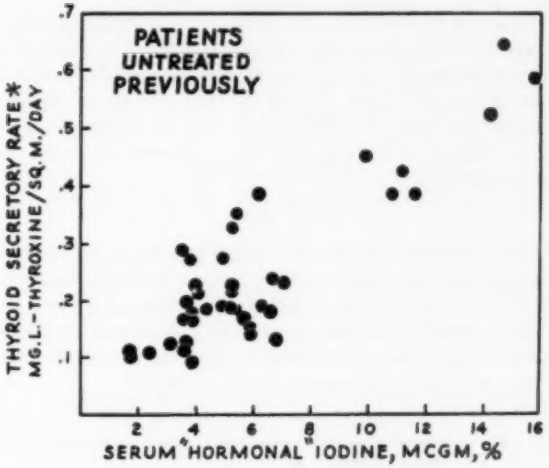

FIG. 3. Thyroid secretory rate, T.S.R., compared with serum "hormonal" iodine in 42 patients.

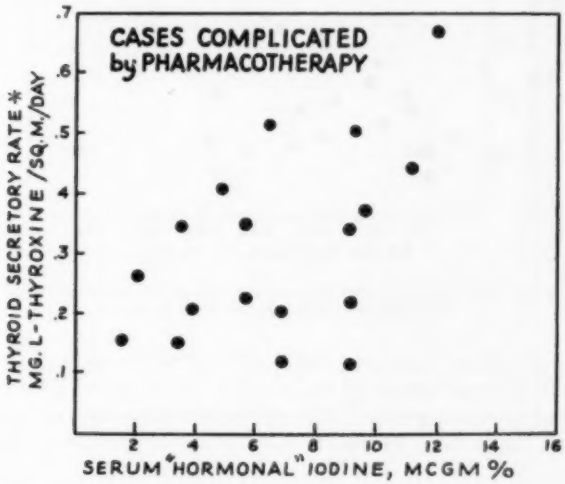

FIG. 4. In contrast to figure 3, the administration of drugs prior to diagnostic appraisal vitiates the correlation of thyroid secretory rate with serum "hormonal" iodine (18 additional patients).

Effect of Drugs

The correlations just described fall awry if the physician injudiciously treats the patient before his thyroid status has been confirmed by laboratory methods. As shown in figure 4, the correlation fails miserably. Other graphs for treated patients (not published) show a similar, but less striking, distortion of the Maximal Uptake and Thyroid Secretory Rate (both determined by radioactivity).

Discussion

Several large series of patients have been presented in the literature [5, 6, 7] from the standpoint of laboratory confirmation. In these, however, the four chief diagnostic procedures (discussed in this report) have not been correlated one with another. Furthermore, the rather low correlations previously published suggest that uncontrolled variables creep into large groups of data and tend to distort fundamental relationships.

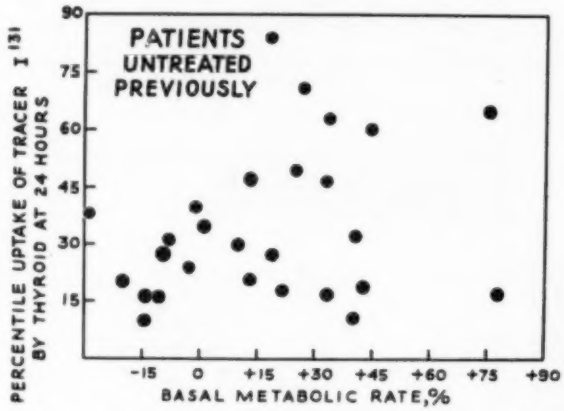

Fig. 5. Very poor correlation is noted between the 24-hour percentile uptake of radio-iodide and the basal metabolic rate in 28 patients.

In figure 5, basal metabolic rate is pictured as the chief parameter, correlated with 24-hour uptake of radio-iodide by the gland. The poor correlation is obvious at a glance. The comparison lends support to the concept that serum "hormonal" iodine, S.H.I., is a more reliable "standard" of reference.

Conclusions

In approximately 45 patients the daily thyroxine turnover rate (T.M.R.) was compared with the serum "hormonal" iodine and with measurements

of the uptake of radio-iodide by the thyroid gland. It was found that the protein-bound iodine of the serum correlated well with the estimated thyroid secretory rate (T.S.R.). Such observations are more consistent than B.M.R. and 24-hour percentile uptake, but only when established in untreated patients. The data help distinguish hyperplasia from hyperfunction in the goitrous patient.

ACKNOWLEDGMENT

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THE PERIPHERAL VASCULAR LESIONS OF LUPUS ERYTHEMATOSUS * †

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Since the initial report in 1935 by Baehr and associates [1] of the diffuse peripheral vascular involvement in lupus erythematosus, much histologic investigation has been directed toward clarifying the nature and extent of this process. Initially it was the impression of these investigators that it was primarily a process of endothelial proliferation associated with narrowing and occlusion of small vessels. Subsequently, in 1941, Klemperer and his group of workers [2] clarified this misconception, and introduced the concept of fibrinous degeneration. It was proposed that in lupus erythematosus, collagen diffusely underwent a degenerative change as a result of an "X" stimulus, and, because of the diffuse distribution of the mesenchymal tissue, the changes were accordingly widespread in many systems. The fibrinoid change, according to Klemperer, could be one of two types: (1) initial swelling with secondary cellular reaction and subsequent sclerosis, or (2) sclerosis first without preceding reaction. The difference in response was probably modified by the intensity and tempo of the inflicting force. The vascular changes noted were mainly in the smaller vessels and arterioles. Venous changes were reported as uncommon in the tissues examined, and little note was made of muscle, peripheral nerve and synovial tissue.

Clinically, arthralgias are common symptoms of patients with lupus erythematosus. Slocumb [3] reported the incidence of arthritic manifestations in chronic, subacute and acute forms to be 20, 57 and 63 per cent, respectively, and in more than 50 per cent of the cases manifestations involving joints preceded the appearance of lesions involving the skin by from one and a half months to five years. More recently, Montgomery and McCreight [4] have reported an incidence of arthralgia-arthritis in the chronic, subacute and acute forms of 43, 71 and 91 per cent, respectively; they attribute this increase in manifestations in joints to a more acute awareness of the arthralgia in the earlier clinical diagnosis of lupus erythematosus. Despite this prominent feature, little histologic investigation of synovial changes in the disease has been carried out. It has been noted that, while synovial involvement is frequent, the development of a progressive deforming arthritis is

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† Microscopic studies of tissue were done in the laboratory of Dr. James W. Kernohan and under his supervision.

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rare. Slocumb noted it in one of 10 cases. If deformities do occur, they usually do so late in the course of the disease. According to Friedberg and co-workers, the smaller joints are most frequently involved,[8] though larger joints may be affected.

In one case of lupus erythematosus, Mallory [6] reported that the patient's joints showed evidence of severe synovitis but "no evidence of rheumatoid arthritis." In the case reported by Ginzler and Fox,[7] slight hyperplasia was noted in some areas of joint synovia, but inflammation or vascular alteration was not evident. Hypertrophy of synovial villi, inflammation of synovia and perivascular inflammation in subsynovial and capsular tissues have been noted by Cluxton and Krause.[8]

Microscopic studies of muscle in cases of lupus erythematosus have been few and incomplete. Most observations have been made incidentally, in cases in which patients who had lupus erythematosus were used as controls in recent studies of changes in muscles of patients having rheumatoid arthritis. Clawson and co-workers [9] reported that in the case of lupus erythematosus which they studied, six of seven muscles showed evidence of myositis, and the lesions were not of the fibrinoid nature so commonly referred to as the specific reaction in lupus erythematosus. Bunim and associates [10] noted typical nodular lesions of muscle in one of two cases of lupus erythematosus. Atrophy, irregular degenerative changes of muscle fibers and occasional mild interstitial inflammation were noted in sections of voluntary muscle in one case reported by Ginzler and Fox.[7] In five cases, Klemperer and co-workers [2] examined skeletal muscle and noted mild perivascular round-cell infiltrations which were not considered to be of significance. In a sixth case, however, intense interstitial and perivascular round-cell reaction plus myositis of the psoas and rectus muscles were noted. Fibroblastic proliferation or regeneration in the vascular walls with perivascular round-cell infiltration in skeletal muscle was noted by Correa [11] in two cases of another series.

Method

All tissue was obtained at necropsy. The primary cause of death in each case was lupus erythematosus. Muscle was available in 15 cases, peripheral nerve material in 15 cases and synovial tissue in five cases. Diaphragms which showed serositis were excluded from the study because of the high concomitant incidence of bronchopneumonia. Tissue was embedded in paraffin blocks, and serial sections, 8 micra in thickness, were prepared; a minimum of 300 sections was cut from each block, and every tenth section was mounted and stained for study. Hematoxylin and eosin, Mallory's phosphotungstic acid and van Gieson's and Mallory-Heidenhain's stains were employed. Adequate material for serial sections of at least one muscle and one peripheral nerve was prerequisite to inclusion of the case in the study. If available, additional specimens of muscles and nerves and

specimens of synovial tissue were prepared in serial or less exhaustive serial sections for study and comparison.

As controls, muscles and nerves were obtained at 30 routine necropsies and prepared in a manner identical to that described. Ready availability made it possible to obtain multiple samples of muscles and nerves. Four cases of leukemia, one of acrosclerosis and one of periarteritis nodosa were eliminated from the control group because of known vascular changes, but other cases were unselected and included those in which changes in muscle and nerve were known to exist.

Observations (Table 1)

Degeneration of Muscle. Degeneration was noted in 11 (73 per cent) of the 15 muscles serially sectioned. In addition, degeneration was seen in a single section from each of two other muscles; in some muscle, therefore, in 13 of the cases, there was evidence of muscle degeneration. In all, a total

Table 1

Peripheral Vascular Lesions Noted in Serial Sections of Muscle and Nerve

	Lupus erythematosus (15 cases)		Controls (30 cases)	
	Muscle, per cent	Nerve, per cent	Muscle, per cent	Nerve, per cent
Degeneration	73	53	37	37
Perivascular cell aggregates	100	93	13	10
Arterial changes:				
Active	Occasional	7	10	10
Old	0	13	27	10
Venous changes:				
Edematous phase	13	Occasional	3	0
Reactive phase	100	93	0	0
Sclerotic phase	46	73	33	37

of 62 muscles in the 15 cases were studied, an average of 4.1 different muscles per case. Degeneration was noted in 50 (81 per cent) of the 62 muscles. It varied from early loss of striations or spotty degenerative changes in single bundles to extensive new or old involvement of muscle. This was graded on a scale of 1 plus to 4 plus, the former indicating 25 per cent involvement and the latter 100 per cent involvement. Ten per cent showed occasional changes, 38 per cent were graded 1 plus, 40 per cent were graded 2 plus, 10 per cent were graded 3 plus and 2 per cent were graded 4 plus.

Of the 30 control cases, 11 of the 30 serially sectioned muscles (37 per cent) showed degenerative changes of comparable degree.

Perivascular Cell Aggregates. In Muscles. Perivascular cell aggregates in muscles were found in one or more specimens in all 15 cases (100 per cent) of lupus erythematosus. Of the single specimens serially sec-

tioned for study, those from 13 of the 15 muscles (87 per cent) were positive. Of the 62 muscles studied in the 15 cases, 35 (56 per cent) showed collections of nodular perivascular cells in one or more sections.

In the 30 control cases, aggregates of perivascular cells were found in only four cases (13 per cent). A total of 240 different muscles from the 30 cases were studied, and only five specimens (2 per cent) showed perivascular aggregates.

In Nerves. In 14 (93 per cent) of the 15 cases of lupus erythematosus, nerves showed perivascular cell aggregates. In the 15 cases, a total of 27 different nerves were studied and 21 (78 per cent) showed aggregates of perivascular cells. In one case, nodules were not present in any nerve section. In the group of controls, three (10 per cent) of the 30 nerves studied serially showed cell aggregates. A total, however, of 110 nerves were sectioned and studied from the 30 cases, and only the three mentioned (3 per cent) showed positive findings. In these three cases a total of eight additional nerves were studied but cell aggregates were not present.

The incidence of nodules in muscles and nerves in individual cases tended to correlate statistically, but the sizes of nodules from muscle to muscle and muscle to nerve varied considerably. Cell aggregates were tabulated on a basis of quantity; less than 25 cells was disregarded, the presence of 25 to 49 was considered as 1 plus, of 50 to 74 as 2 plus, of 75 to 99 as 3 plus and of 100 or more as 4 plus.

Degeneration of Nerves. Small to medium-sized areas of localized degeneration of nerves were noted in 53 per cent of the 15 cases of lupus erythematosus and in nine (33 per cent) of the total of 27 nerves studied. Among controls, degeneration occurred in 11 (37 per cent) of 30 cases and in 19 (17 per cent) of 110 nerves studied. A study of the cases revealed that 60 per cent of the 19 nerves were from two patients who had had hypertension, one who had had poliomyelitis and one who had had subacute bacterial endocarditis.

Vascular Changes. These changes were subdivided into four main groups; namely, arteritis, phlebitis, fibrinoid degeneration and endothelial proliferation. Arteritis was classified as active or old, and phlebitis was subgrouped into one of three phases: the edematous, the reactive or the sclerotic. The edematous phase of the latter showed acute swelling of the vascular wall without cellular reaction. The reactive phase was one of residual swelling or thickening, plus a cellular response within and about the vascular wall. Sclerosis indicated a hyaline-like thickening of the wall of the vein without residual cellular aggregation.

Considerable evidence of the edematous phase of phlebitis was found in the veins in sections of muscles from two cases of lupus erythematosus and from a few nerves. Evidence of the reactive phase was notable in muscle in every case and in sections of nerves from 93 per cent of the cases. All aggregates of perivascular cells were closely associated with this stage

of vascular change. The sclerotic stage was apparent in muscle from 46 per cent and in nerves from 73 per cent of the cases.

Arterial changes were uncommon except in controls, in which they were evident in 27 per cent.

Material which suggested fibrinoid degeneration was found in only one section of muscle from one case of lupus erythematosus.

Instances of endothelial proliferation were not noted.

Synovial Tissue. Synovial tissue was studied in five cases. Tissue from single joints which were or had been involved was available in four cases, while in the fifth case, synovia was obtained both from a joint in which involvement by lupus erythematosus had recently subsided and from a joint which was currently involved. From a clinical standpoint, this spread provided an opportunity for correlating a determining pattern of progressive synovial involvement. In all cases, vascular change was a notable feature. Venous changes varying from the acute edematous to the sclerotic phase of phlebitis were present in each of the six specimens. In three of the six samples, arteries also were involved with swelling and luminal encroachment, in one case to the extent of complete occlusion. In two of the six cases, perivascular cell aggregates were present. Stromal changes varied from edematous separation of connective tissue fibers to heavy old organized fibrosis. Synovial lining cells were little affected, except for mild hyperplasia in some instances.

Comment

Degeneration of muscle in our cases of lupus erythematosus occurred more frequently than is normal. Usually degeneration was of slight to moderate degree, and it appeared focally or in a disseminated pattern. It was impossible to correlate the focal degeneration with the focal vascular embarrassment, although this pattern of reaction was suspected in several instances (figure 1). Degeneration varied from early loss of striations to old "falling out" of muscular tissue with fibrotic replacement, and it was noted that degenerative changes varied from muscle to muscle in the same case. The degree of degeneration roughly paralleled vascular involvement in occurrence but not in degree; complete dissociation of the two phenomena, that is, degeneration of muscle and vascular changes was not noted in any instance. In view of Clawson and associates'[9] much lower incidence (42.3 per cent) of degeneration of muscle in their study of muscles obtained at 450 routine necropsies, the high incidence of degeneration (73 per cent) which we noted in cases of lupus erythematosus in our series would indicate that muscular changes are significant components of the disease process.

In the control cases, fatal disease processes such as subacute bacterial endocarditis, hemiplegia, poliomyelitis, peritonitis, pemphigus, chronic ulcerative colitis and malignant hypertension usually accounted for degeneration of muscle. On examination of seven muscles in each of their 450 unselected cases, Clawson and others found that a grade of atrophy of 1 plus or more

was observed in one or more muscles in 191 (42 per cent); the incidence of 37 per cent in our control series of 30 cases is in keeping with their findings.

Vascular involvement in muscular and nervous tissue in cases of lupus erythematosus was widespread and a characteristic finding. It was typical in that venous involvement predominated, with only occasional involvement manifest on the arterial side of the circulation; in tissue in which arterial involvement occurred, the process appeared to be profound on the venous side. In both of these types of tissue the pattern of the vascular process was identical. It appeared that the initial phase was acute edematous phlebitis, in which the venous walls were thickened and hydropic in appearance and the cells were swollen. Granular eosinophilic "dust" was stippled through the walls of these vessels (figure 2). This progressed,

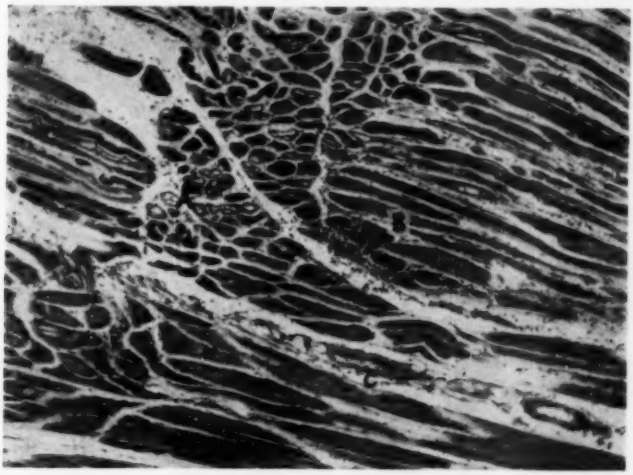

FIG. 1. Degeneration of muscle, showing old "falling out" of muscle (A), active degeneration (B), and vascular reaction (C) (hematoxylin and eosin, × 50).

it seemed, to a secondary reactive phase, in which the venous wall was undergoing a reactive reparative process as evidenced by the presence of many cells within and about the wall. Aggregates of perivascular cells occurred frequently. Lesions early showed a central zone of large mononuclear cells having vesicular nuclei and an outer zone of lymphocytes in a ratio of about 1:1. Fibroblasts were evident, and, peripherally, occasional plasma cells and infrequent eosinophilic polymorphonuclear leukocytes were noted (figure 3). In older reactive lesions the mononuclear cells were less numerous or absent, as were the fibroblasts, and a collar of lymphocytes was left within and without a condensed thickened venous wall. In serial sections it was

evident that a perivascular nodular reaction involved only sections of the same vessel; usually this nodular involvement extended along the vessel for short distances, but in others the involvement was extensive. Not uncommonly, the reaction involved only a portion of the circumference of the vascular wall, and in such instances the swelling and the cellular aggregation with the ultimate sclerotic thickening were confined to the involved portion of the wall. Nodules were not seen about arteries in any of the sections. In the third phase, the cell aggregates were gone, and there remained a vascular wall with sclerotic thickening varying in degree from slight to marked (figure 4). Varying phases of this vascular pattern were present

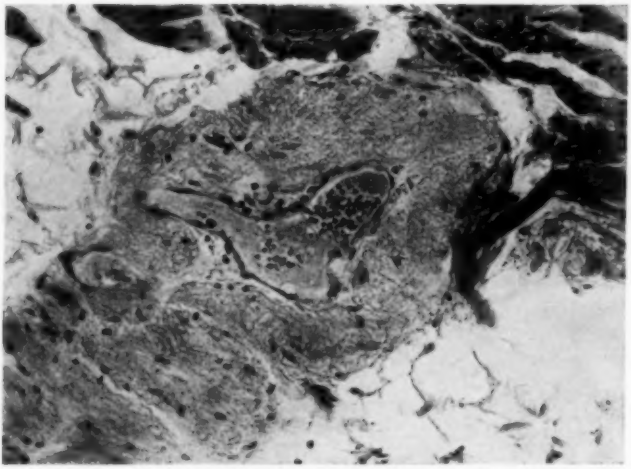

FIG. 2. Vein showing acute edematous phlebitis and eosinophilic stippling (hematoxylin and eosin, × 215).

in most sections; in muscles and in nerves, sclerotic vessels frequently were observed in sections which also showed cellular reaction. It cannot be assumed, however, that the sclerotic phase is necessarily the end result of the reactive phase, particularly in view of the thesis [2] that a variation in tempo and intensity of injury may effect sclerosis directly.

In the control group of cases the reactive pattern of vascular change was not seen. In those sections from the control group in which aggregates of perivascular cells were noted, the aggregates appeared in the adventitia and were not accompanied by concomitant changes in the vascular wall. In one control case, in which the patient had had carcinoma of the esophagus and had died in shock during operation, acute edematous changes were evident in veins without cellular reaction. This provides interesting specu-

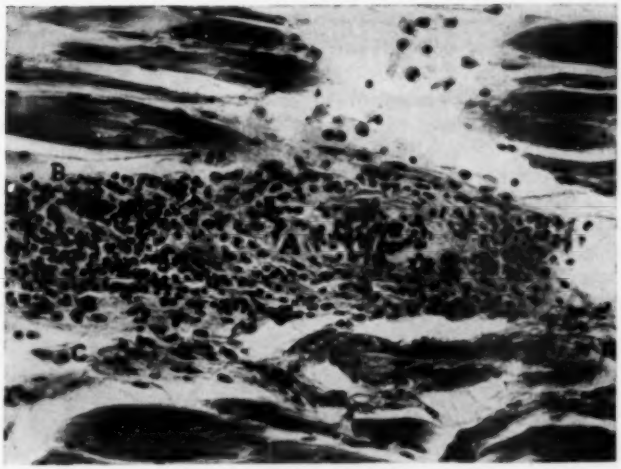

FIG. 3. Vein showing reactive phase of phlebitis with mononuclear response (A), lymphocytic cuff (B), and scattered plasma cells and fibroblasts (C) (hematoxylin and eosin, × 245).

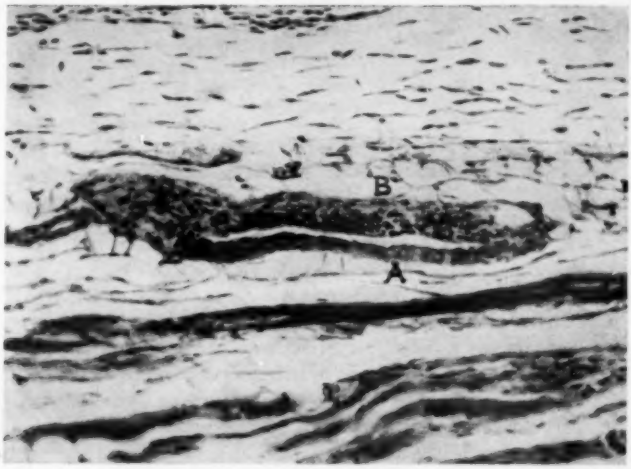

FIG. 4. Vein showing sclerosis of one wall (A), and persisting cellular reaction of the opposing wall (B) (hematoxylin and eosin, × 135).

lation as to the significance of a vascular reaction such as has been observed in this study.

The significance of the high percentage of cases of lupus erythematosus (53 per cent) and of individual nerves (33 per cent) from these cases showing degenerative changes is difficult to evaluate. By comparison, however, with the incidence among controls in which poliomyelitis, hypertension, diabetes, subacute bacterial endocarditis and other known causes of focal nerve degeneration were included (37 per cent of cases and 17.3 per cent of nerve specimens), these higher incidences in cases of lupus erythematosus (53 per cent) and of all nerves (33 per cent) would appear to have significance, a suggestion not apparent clinically.

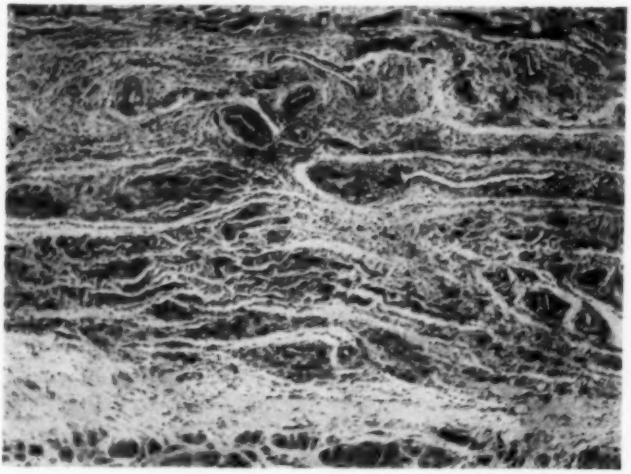

FIG. 5. Synovial section showing swelling of connective tissue and diffuse vasculitis involving all vessels (hematoxylin and eosin, × 50).

The predominant changes noted in the synovia from patients with lupus erythematosus were vascular and stromal. The vessels appeared to be involved in a pattern identical to those of the muscles and nerves. In the more acute phase, edematous swelling of the veins, both large and small, was extreme, and in three of six specimens arteries were similarly involved. This was accompanied by diffuse swelling of the connective tissue stroma (figure 5). The acute phase was followed by a cellular reaction about the involved vessels, similar to but less extensive than that noted in sections of muscles and nerves, and by a fibroblastic stromal response. Numerous young fibroblasts could be seen. Ultimately the vessels either returned to normal appearance or progressed to sclerotic thickening. Similarly, the stromal response in old processes was one of old fibrosis of a greater or less degree,

probably dependent upon the intensity of the initial injury. The lining cells were little affected and showed only mild hyperplasia in several instances.

The aforementioned vascular pattern of reaction is identical to that which we noted in active cases of rheumatoid arthritis. It is similar to the reaction seen in periarteritis nodosa, except that the latter predominantly involves the arterial side of the circulation with a venous overflow, in contrast to the predominant venous involvement in lupus erythematosus. Lesions suggestive of this pattern of reaction have been noted by one of us (Lowman) in four cases of leukemia, a finding which is worth further investigation. Similar lesions have been reported [12] in one case of dermatomyositis, and it was proposed that the latter might be an "angiomyositis" disease. The similarity of vascular damage and reaction in this group of diseases suggests a common pathologic factor. It is of speculative interest that the responses of these diseases to pituitary and adrenal extract may well reflect a nonspecific moderating or reparative process in these damaged vascular systems.

Summary and Conclusions

Serially sectioned muscles in 73 per cent of 15 cases of lupus erythematosus showed slight to moderate degeneration, and 37 per cent of 30 control cases showed similar changes.

In lupus erythematosus, a vascular pattern of reaction on the venous side of the circulatory system appears to consist of three successive phases: edema, cellular reaction and sclerosis. The edematous stage of phlebitis was noted in two cases of lupus erythematosus and in one of the control group, the latter a case of operative shock. The cellular reactive phase, consisting of residual swelling and thickening of the venous wall, together with a cellular reaction of large mononuclear and lymphocytic cells, was noted in some muscle in all cases of lupus erythematosus and in nerves from 93 per cent of the cases. By volume, these were noted in 56.4 per cent of 62 specimens of muscle and in 77.7 per cent of 21 nerves. Similar perivascular aggregations of cells, but without concomitant vascular changes, were noted in muscle from 13 per cent and in nerves from 10 per cent of control cases; by volume, however, only 2.1 per cent of 240 muscles and 2.7 per cent of 110 nerves showed this change.

It would appear that the polymyositic and perineuritic nodules of lupus erythematosus are identical to those seen in rheumatoid arthritis, and that both are produced in this vascular pattern of reaction.

Degeneration of muscle and vascular change could not be correlated in degree. It cannot be concluded whether one is the cause or the consequence of the other, or whether they represent individual reactions to a common stimulus.

The incidence of focal degeneration of nerves was considerably greater in cases of lupus erythematosus than would be expected, but the significance is unknown.

Synovial changes noticed were vascular and identical to the pattern of reaction seen in other tissues; in addition, the stroma showed initial edema with subsequent fibroblastic response and fibrosis. Synovial lining cells showed only mild hyperplasia.

In cases of lupus erythematosus, the vascular reaction identical in nature to that previously observed in cases of rheumatoid arthritis and the similarity of the reaction to that seen in periarteritis suggest a common pathologic factor. There is no clue as to whether the reaction pattern is secondary to damage by an extraneous factor, or whether a hyperergic response is effecting injury to a responding system.

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PULMONARY INFILTRATION WITH EOSINOPHILIA (PIE SYNDROME) *

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Only recently, unsuspected x-ray evidence of nondescript pulmonary infiltrations has focused attention on Loeffler's syndrome, tropical eosinophilia and related conditions. Fewer than 25 case reports of Loeffler's syndrome were found by Peabody [1] in English as recently as 1944. Increased use of chest roentgenography and expanded mass x-ray surveys of the general population should lead to more frequent case reports.

Sir William Osler [2] was probably first to report pulmonary abnormality associated with allergic disease. Then 37 years elapsed before Loeffler's [3] classic report appeared, and 47 years before tropical eosinophilia was described by Weingarten.[4] The clinical description by Loeffler [5] of transient pulmonary infiltration with eosinophilia has stood the test of time. He emphasized variable, migrating infiltrations in the chest roentgenogram and peripheral blood eosinophilia associated with a benign clinical course of brief duration. Pathologic shadows in the chest x-ray film may be bilateral or unilateral, large or small, single or multiple, homogeneous or spotty, and may occupy any part of the pulmonary field. During a two week course, migration, decrease in size and gradual disappearance of the x-ray changes are expected.

Clinical picture and symptomatology vary. Over 25 per cent of Loeffler's original cases were detected during routine chest x-ray examination. Symptoms were lacking. Cough may be severe—either dry or productive of small quantities of white, mucoid sputum. Malaise, anorexia, slight fever and generalized aching may precede the call for medical attention. Expiratory wheezing and dyspnea suggesting bronchial asthma may initiate the attack.

Physical findings are often absent. Occasionally impaired percussion and diminished breath tones are found, with fine or medium moist, crackling râles.[6] Pleural, pericardial and peritoneal effusions containing many eosinophils have occurred.[7] Peripheral blood eosinophilia without immature forms may reach 80 per cent. No correlation exists between degree of eosinophilia and amount, duration or intensity of the pulmonary infiltration.

Tropical eosinophilia, described as a separate entity, is characterized by more pronounced illness and a prolonged clinical course. Onset may occur with anorexia, malaise and a fever of 100° to 101° F. A dry, hacking cough is common, particularly at night.[8] Wheezing and expiratory dyspnea

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may require injection of epinephrine. Occasionally illness begins with an explosive asthmatic attack. Splenomegaly may be detected in 50 per cent of the cases. Roentgenographic findings described by Frimodt-Moller [9] in 175 cases include uniformly distributed, extensive mottling with small, nodular shadows in both lungs. Linear markings were increased, and the diagnosis of a pseudotuberculous condition was advanced. Weingarten's [4] 81 cases evidenced similar findings, with small, ill-defined pulmonary nodules having a blurred periphery and denser center.

Similarities between Loeffler's syndrome and tropical eosinophilia have been noted, and possible relation to other diseases of suspected allergic origin has been mentioned.[10] Original concepts of readily definable entities are changing as more protean cases are encountered.[11-13] Only pulmonary infiltration and blood eosinophilia co-exist in all cases. Specific names, such as Loeffler's syndrome or tropical eosinophilia, seem obsolete. Pulmonary infiltration with eosinophilia (PIE syndrome) has descriptive appeal and, when accompanied by primary, subsidiary or modifying diagnosis, affords a clear word image. Example: PIE syndrome; bronchial asthma. Adoption of the descriptive term PIE syndrome does not offer complete diagnosis or imply therapeutic solution, and this has been emphasized.[14] Use of this term allows inclusion of cases with recurrent and protracted course not logically called Loeffler's syndrome or tropical eosinophilia. Search should be made for accompanying disease of known or suspected allergic origin, especially bronchial asthma, angioneurotic edema, hay fever, eczema, migraine headache, serum sickness, rheumatic fever, rheumatoid arthritis and collagen-vascular diseases. Differential diagnosis in PIE syndrome should include eosinophilic leukemia, Hodgkin's disease, periarteritis nodosa (sometimes an accompanying diagnosis), pulmonary tuberculosis, fat embolism, infectious mononucleosis, septicemia and pneumonia of rheumatic, bronchial, lobar, aspiration or viral type.

We have encountered eight cases with PIE syndrome and various accompanying conditions in 18 months. Four illustrative cases will be presented.

Case Reports

Case 1. A 42 year old white male electrician was admitted October 27, 1950, with excessive fatigue, moderate shortness of breath on exertion and weight loss of 16 pounds in three months. Physical exertion precipitated a cough, wheeze and moderate dyspnea. Nasal stuffiness, rhinorrhea and postnasal drip were present. Anorexia, malaise and generalized muscular aching varied in duration and severity. Nocturnal sweating was not accompanied by chills or fever until the day before admission. Previous therapy by the family physician was symptomatic, for a head cold and excision of nasal polypi. Exposure to inhalation injury and past illness was denied. Hives in childhood constituted the only previous allergic experience.

The patient was using the accessory muscles of respiration. Temperature, 102.4° F.; pulse, 120 per minute; respirations, 20. Slightly impaired resonance and reduced tactile fremitus at the right base posteriorly accompanied scattered, dry, musical, inspiratory and expiratory râles. An expiratory buzz was heard at the open

mouth. Blood pressure was 110/64 mm. of Hg, right arm, supine, and 115/70 mm. of Hg in left arm. Remaining findings were normal.

Urinalysis was normal. Blood non-protein nitrogen and sugar were not elevated, and Kline exclusion test was negative. Sedimentation rate was 35 mm. (Wintrobe) in one hour; hematocrit, 41. Hemoglobin was 12.7 gm.; red blood cells, 4.19 million, and white blood cells, 11,150, with 45 per cent polymorphonuclears, 16 per cent lymphocytes, 2 per cent basophiles, 1 per cent mononuclears and 36 per cent mature eosinophils. Repeated in 48 hours, total white blood cell count was unchanged. Admission blood culture and cold agglutinins were negative. No acid-fast bacilli were seen in three consecutive daily sputa and one gastric washing. *Neisseria catarrhalis*, nonhemolytic streptococcus and coagulase-negative *Staphylococcus albus* were cultured from initial sputum.

On admission, roentgenographic examination of the thorax revealed a normal cardiovascular silhouette, with hilar shadows of moderate size and thickening of both apical caps. A small, patchy, irregularly rounded area of infiltration with a fuzzy periphery was noted in the right lower lung near the costophrenic angle. A round, calcific density was present in the right perihilar area.

Mild urticaria developed 24 hours after intramuscular penicillin and streptomycin, and promptly subsided when these were discontinued and Benadryl was administered. Seven days of oral aureomycin did not result in clinical improvement, but the patient left the hospital before completion of diagnostic studies.

He returned two weeks later (November 19) with chills, fever, night sweats, malaise and a cough productive of white, mucoid sputum, present for one week. Temperature, 101.4° F.; pulse, 100; respiratory rate, 18. Abnormal findings were limited to bronchovesicular breath tones over the right apex posteriorly and a few scattered, expiratory wheezes and snores. Blood chemistry, electrocardiogram, urinalysis and sputum examinations were again normal. Stained sputum revealed a predominance of eosinophils. Leukocyte count was 30,900, with 38 per cent polymorphonuclears, 10 per cent lymphocytes, 3 per cent monocytes and 38 per cent mature eosinophils.

Chest roentgenogram revealed extensive, patchy, parenchymatous infiltration throughout the right lung, densest in the middle third. Similar involvement extended below the clavicles in the axillary line on the left, with a small area in the left apex. Previously visualized infiltration at the right costophrenic angle had disappeared.

Two gastric washings did not reveal acid-fast bacilli by smear or culture. Blood cold agglutinins remained negative. Oral chloromycetin in usual doses for one week did not accomplish reduction of fever or affect symptoms or physical findings. Direct eosinophil count on November 29 was 6,259, and 53 per cent of 18,500 leukocytes were eosinophils. Sternal marrow revealed increased eosinophil production without abnormal or immature forms. Repeated stool examination did not reveal ova or parasites.

Chest x-ray film of November 29 demonstrated slight progression of the process on the right, with increased infiltration, particularly in the middle third (figure 1).

Clinical impression of PIE syndrome, urticaria and probable bronchial asthma seemed justified. Twenty-five milligrams of a saline suspension of cortisone was begun by aerosol technic every two hours on November 29 and continued every four hours after the first five doses. Chloromycetin was continued in 250 mg. doses at four hour intervals for the next two days. Within four hours, temperature was normal and remained so (chart 1). Symptoms had largely disappeared in eight hours and completely in 24 hours. Breathing without audible buzz and absence of abnormal physical findings occurred within 48 hours. Direct eosinophil count fell from the pretreatment level of 6,259 to 2,765 by the third day of cortisone inhalation, and total leukocytes were 15,800. No evidence of irritation to oropharynx was evident from cortisone inhalation.

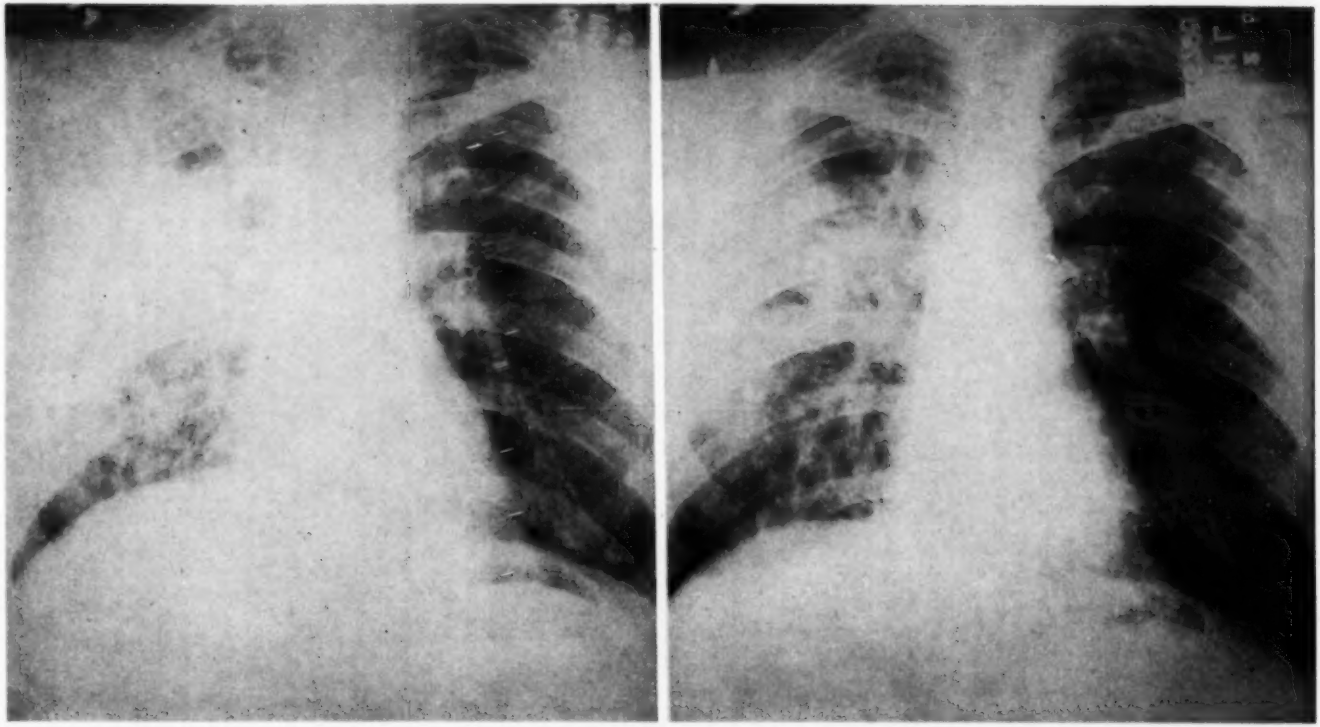

FIG. 1 (*left*). *Case 1.* Chest roentgenogram on second admission prior to cortisone. Extensive patchy infiltration both lungs.
FIG. 2 (*right*). *Case 1.* Chest roentgenogram on third day of cortisone administration. Infiltration less dense and extensive.

Chest roentgenogram on the third day of cortisone administration indicated beginning, definite clearing of infiltration, especially in the base of the right upper lobe (figure 2), and the patient was allowed to go home. Nebulized cortisone was continued at home, and symptomatic improvement was maintained. On December 16, direct eosinophil count was 158 and total leukocyte count was 9,850, with 50 per cent polymorphonuclears, 45 per cent lymphocytes and 5 per cent eosinophils. Withdrawal of cortisone resulted in no untoward symptoms. Radiographic evidence of almost

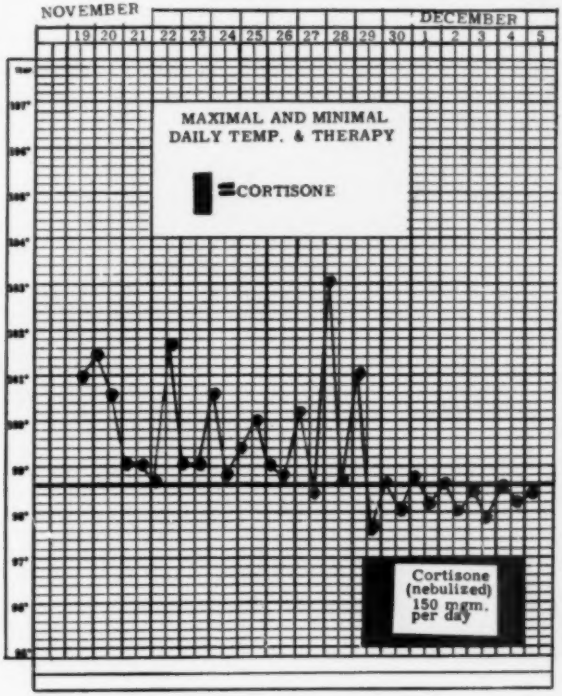

CHART 1. *Case 1.*

complete resolution of pulmonary infiltration had occurred by the time the drug was discontinued (figure 3), after a total dose of 2,325 mg. had been administered in 17 days.

The patient returned to work the day the drug was discontinued and continued to feel well except for occasional mild attacks of bronchial asthma. Chest x-ray and blood counts were normal in January, 1951. When last seen, in May, 1951, symptoms were absent, physical findings were normal and leukocyte and direct eosinophil counts were not elevated. Chest roentgenographic findings continued normal (figure 4). Allergic investigation, including skin tests, is to be done.

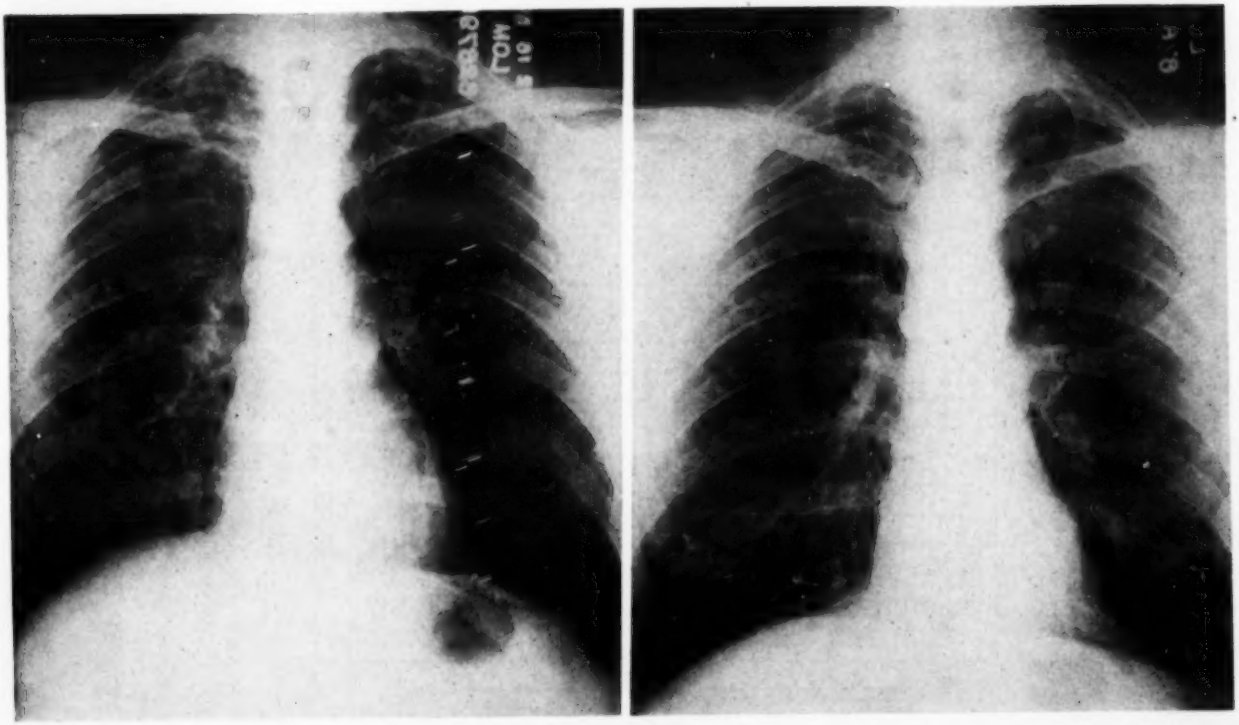

FIG. 3 (*left*). *Case 1.* Chest roentgenogram at time cortisone was discontinued, after 17 days; 2,025 mg. were given. Infiltration has almost completely disappeared.

FIG. 4 (*right*). *Case 1.* Progress chest roentgenogram five months after illness.

Comment: Symptoms and physical and radiographic findings were initially suggestive of viral pneumonitis, for which antibiotics were given. Original eosinophilia was not reported in a repeat leukocyte count the day following the admission; however, subsequent persistent eosinophilia suggests laboratory error. A high index of suspicion and correlation of clinical, x-ray and laboratory data could have resulted in an earlier diagnosis of PIE syndrome and its accompaniment before the patient left the hospital on the first admission.

Experience with nebulized cortisone by one of us (Reeder) [15] has shown this to be an effective route of administration, without demonstrable irritation to trachea or bronchi. It possesses no advantage over the parenteral route.

Case 2. A 65 year old white housewife was first seen in the Allergy Clinic March 26, 1951, complaining of wheezing and moderate shortness of breath, intermittent cough productive of white, mucoid sputum, excessive fatigue with anorexia, and weight loss of 23 pounds. Symptoms were of one year's duration. Past illnesses, including hives, hay fever, asthma, eczema, migraine headaches and food intolerance, were denied.

Dark circles were present under the eyes and there was evidence of recent weight loss. Oral temperature, 99.4° F.; pulse, 92; respirations, 20 per minute. A faint, expiratory buzz was heard at the open mouth. Expansion was uniformly slightly limited, and the chest was hyperresonant to percussion. Scattered, dry, expiratory wheezes and musical râles were heard throughout both lung fields. Blood pressure was 130/84 mm. of Hg in the right arm, supine; 136/86 mm. of Hg in the left. Cardiac findings, including electrocardiogram, were normal, as were other physical features except for varicose veins in both lower legs. Skin tests indicated moderate sensitivity to house dust without other positive reactions.

The patient was admitted to hospital April 12, 1951. Symptoms and physical findings were unchanged. Blood non-protein nitrogen and sugar were normal; Kline test was negative. Red blood cells were 4.73 million; hemoglobin, 15.6 gm.; leukocyte count, 19,000, with 33 per cent polymorphonuclears, 26 per cent lymphocytes, 1 per cent monocytes and 40 per cent mature eosinophils. No "L. E. cells" were seen in sternal marrow, which contained 38 per cent eosinophils and precursors in normal ratio. Sedimentation rate was 20 mm. (Wintrobe) in one hour, and hematocrit was 37. Venous pressure, Decholin and ether circulation times were not elevated. Urinalysis demonstrated no abnormality. Repeated examination of warm stools did not reveal parasites or ova.

Chest roentgenogram revealed a prominent cardiac silhouette and aortic knob with some increase in hilar shadows. Bronchovascular markings were accentuated, and an ill-defined, fleecy infiltration with irregular borders occupied the midportion of each second intercostal space (figure 5).

Clinical impression was PIE syndrome, generalized arteriosclerosis, pulmonary emphysema and bronchial asthma. Congestive heart failure was considered. ACTH, 20 mg. intramuscularly every four hours, was begun on April 8. Within six hours breathing was easier and fewer râles were audible. Twenty-four hours later appetite had returned, with freedom from symptoms. Physical findings were negative and pulmonary infiltration was less (figure 6). Previously normal temperature continued. Direct eosinophil count of 4,569 when ACTH was begun had decreased to 1,357 two days later. On the fifth day it was reduced to 21, with a total leukocyte

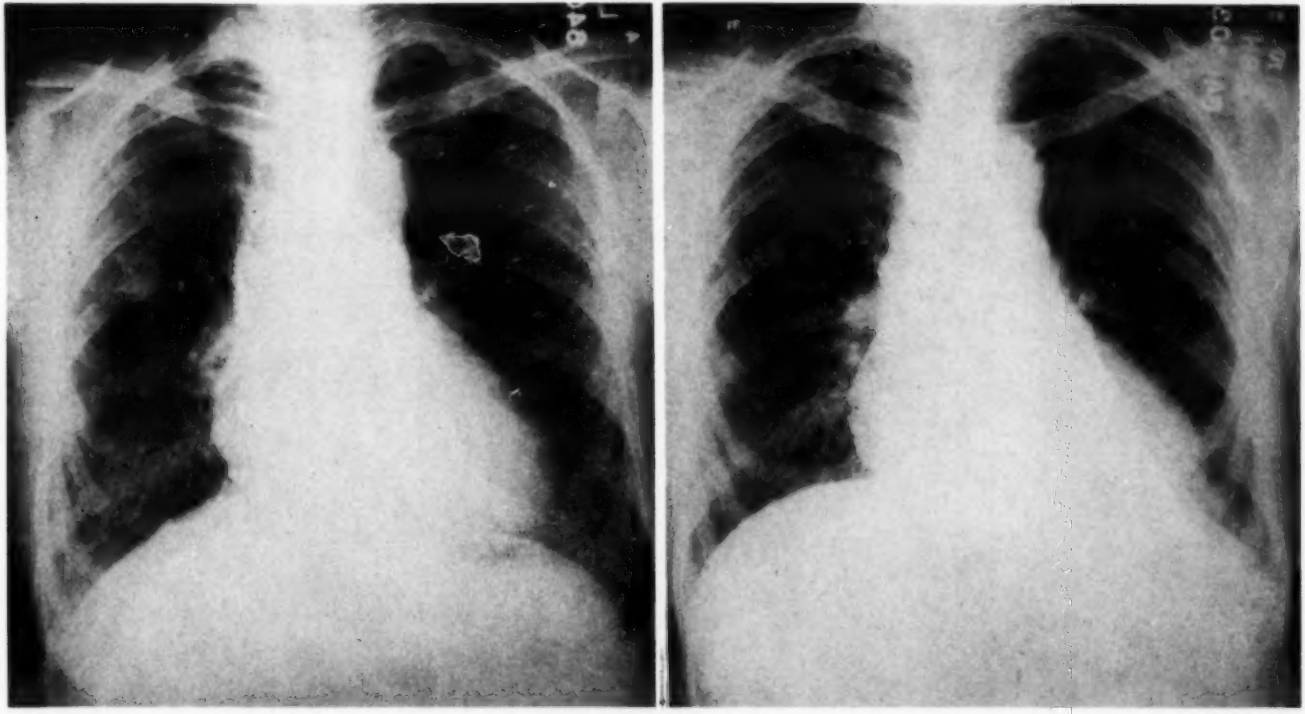

FIG. 5 (*left*). *Case 2.* Admission chest roentgenogram. Cardiac shadow and aortic knob are prominent. Bronchovascular markings are increased, and an ill-defined fleecy infiltration is seen in each second intercostal space.

FIG. 6 (*right*). *Case 2.* Chest roentgenogram after 24 hours of ACTH. Infiltration clearing.

count of 5,300, of which 76 per cent were polymorphonuclears, 21 per cent lymphocytes and 3 per cent mature eosinophils. Chest roentgenogram evidenced resolution of infiltration by the fifth day of ACTH administration (figure 7).

Gradual withdrawal of ACTH was begun after 10 days of treatment, and discontinuance occurred without untoward symptoms on the thirteenth day, after a total dose of 1,170 mg. A 10 pound weight gain occurred without salt restriction, but blood pressures remained down. When discharged, symptoms, physical findings and hemogram were normal. Three weeks after discharge the weight was constant, symptoms were absent, blood count was normal, and no infiltration was demonstrated in the chest roentgenogram.

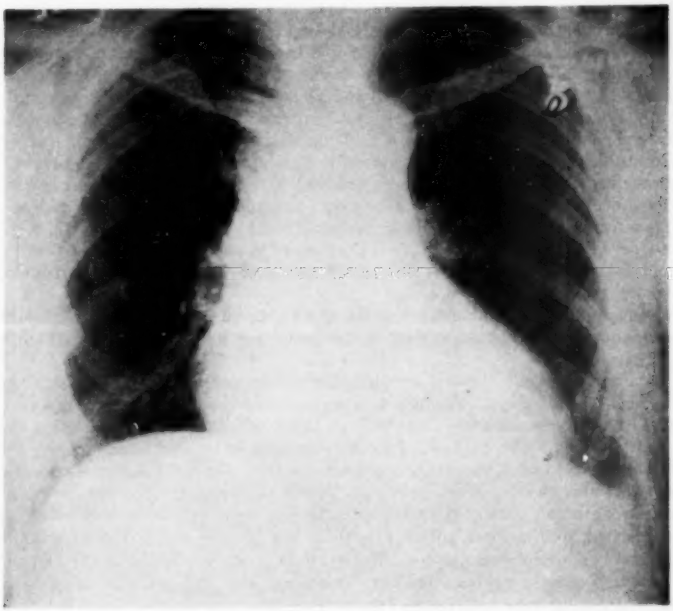

FIG. 7. *Case 2.* Chest roentgenogram on fifth day of ACTH therapy. Infiltration has disappeared.

Comment: Prompt alleviation of symptoms and roentgenographic clearing of pulmonary infiltration seemed related to institution of ACTH therapy, although spontaneous remission cannot be unequivocally denied.

Cases 1 and 2 seem to represent PIE syndrome without accompanying severe, progressive disease. A reversible process without demonstrable residual was evident.

Case 3. A 35 year old white male salesman was admitted March 31, 1950, with cough and hemoptysis of three weeks' duration. Nocturnal sweating without fever had accompanied a cough productive of white, mucoid sputum, occasionally streaked

with bright red blood. Muscular aching was present in arms and legs. The right eye felt "scratchy," was red and had been tearing for two weeks. Impaired hearing and tinnitus had annoyed him since a right simple mastoidectomy elsewhere three months previously. Anorexia and malaise had accompanied a weight loss of 15 pounds in two months. Previous chest roentgenogram by the family physician was said to indicate possible tuberculosis.

Conjunctival injection without obvious infection in the right eye was observed in a well developed, well nourished patient in no acute distress. Funduscopic examination was normal and pupils reacted equally to light. Healed postauricular scar on the right and mild conduction deafness were present. Other physical findings were not abnormal.

Oral temperature, 100.2° F.; pulse, 94; respiratory rate, 20 per minute. Electrocardiogram, blood non-protein nitrogen and sugar were normal. A trace of albumin, 10 to 15 red blood cells and 2 to 5 cellular and hyaline casts per high power field were seen in urine. Sedimentation rate was 35 mm. (Wintrobe) in one hour, and hematocrit was 42. Hemolytic streptococcus and *Streptococcus viridans* were cultured from sputum. Four direct smears of sputa, two cultures and two guinea pig inoculations failed to demonstrate acid-fast bacilli. Bronchoscopy revealed a small quantity of blood and thick yellow secretions draining from a secondary orifice of the right upper lobe bronchus. Culture of secretions from this area produced *Streptococcus viridans*, and Papanicolaou smear of these secretions and sputa did not reveal cancer cells. Red blood cell count was 3.84 million; hemoglobin, 11.9 gm.; leukocyte count, 17,651, with 61 per cent polymorphonuclears, 14 per cent lymphocytes and 25 per cent mature eosinophils. Sternal marrow contained 28 per cent eosinophils and precursors in normal ratio.

Roentgenographic examination of the chest showed a bilateral patchy infiltration with ill-defined borders, most evident in the lower portion of the right and left upper lobe (figure 8).

Intramuscular penicillin and streptomycin did not influence symptoms or recurrent spiking fever for 10 days. Anemia, leukocytosis and eosinophilia to 59 per cent persisted, with albuminuria, a few casts and red blood cells in the urine. Plasma albumin was 3.93 gm., and globulin, 3.15. Flocculation tests of hepatic function were normal. Stained sputa contained eosinophils predominantly. Repeated warm stools did not contain parasites or ova. First strength purified protein derivative was negative and second strength moderately positive. Trichinella skin tests were negative. Symptoms persisted, with a three pound weight loss in 10 days. Local therapy with zinc sulfate and neo-synephrine did not affect symptoms or appearance of the right eye.

Progress chest x-ray examinations one week and 10 days after admission disclosed a persisting hazy infiltration (figure 9). Direct eosinophil count was 2,436 on April 14, and 22 per cent of 15,700 leukocytes were eosinophils.

Clinical impression was PIE syndrome and possible periarteritis nodosa, though a gastrocnemius muscle biopsy did not reveal confirmatory pathology. On the fifteenth hospital day (April 14), ACTH was begun, 20 mg. intramuscularly at six hour intervals, and antibiotics were discontinued. Temperature soon became normal (chart 2). Appetite returned but weight remained unchanged. Twenty-four hours after ACTH was started, direct eosinophil count was reduced from 2,436 to 891, and on the third day the leukocyte count had fallen from 15,700, with 22 per cent eosinophils, to 13,750, with 3 per cent eosinophils. Urine continued to show a trace of albumin and a few red blood cells and casts. No eosinophils were seen in the direct count on the fourth day of ACTH, and total leukocyte count was 14,900, with 80 per cent polymorphonuclears and 20 per cent lymphocytes. Blood sugar was not elevated. Albumin was 3.39 and globulin 3.04 gm. on the fifth day of ACTH. After

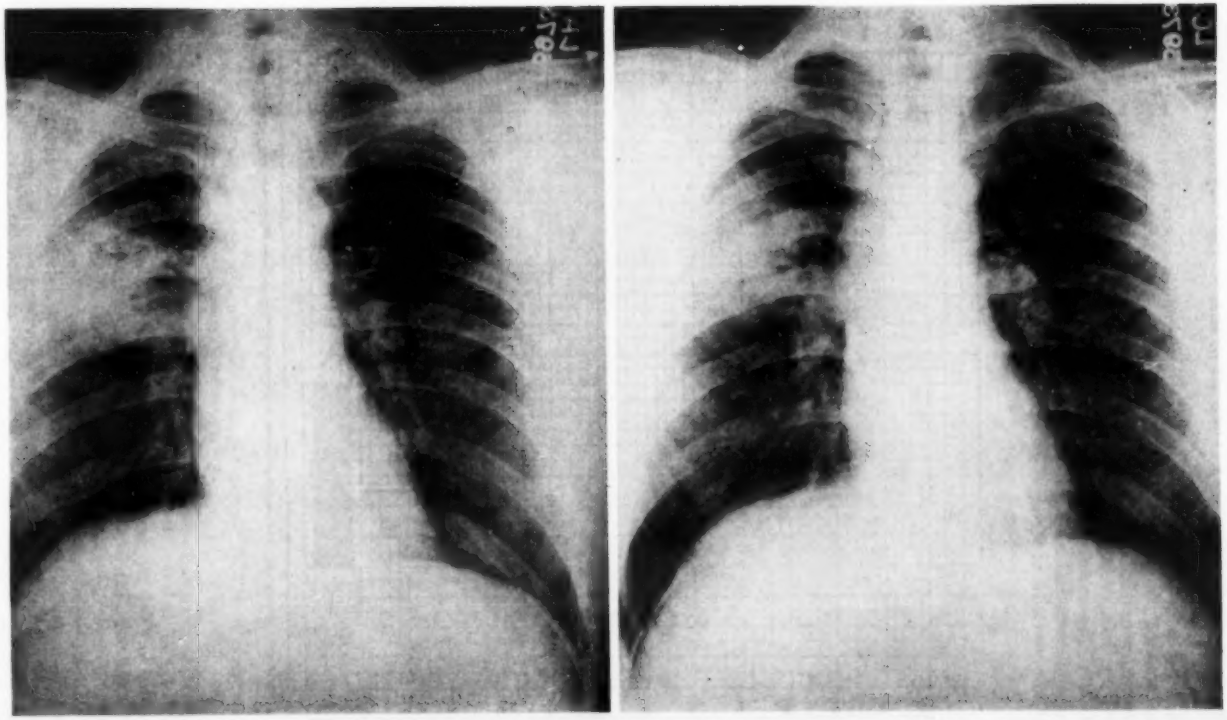

FIG. 8 (*left*). *Case 3.* Admission chest roentgenogram. Bilateral, patchy infiltration most marked in mid lung field on right.
FIG. 9 (*right*). *Case 3.* Chest roentgenogram nine days after admission. Persisting infiltration not influenced by antibiotics.

the first day of hormone therapy the patient became symptom-free. The right eye appeared normal.

Roentgenographic evidence of subsiding infiltration was available three days after ACTH was started, and marked change was seen after six days (figure 10). After six days ACTH was discontinued because the supply was exhausted. Four hundred twenty milligrams had been administered. Two days later symptoms began to recur. Fever, conjunctivitis in the right eye, generalized muscular aching, malaise, anorexia

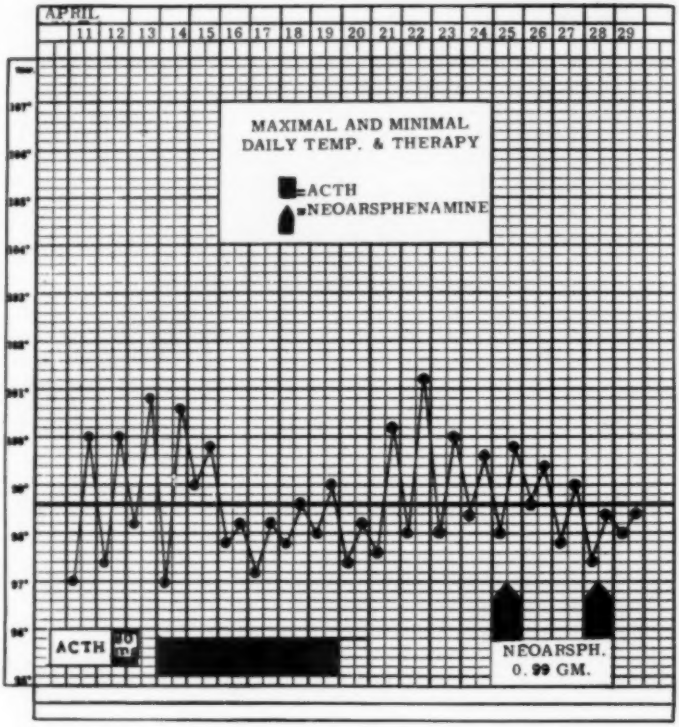

CHART 2. *Case 3.*

and sweating were accompanied by a sharp increase in eosinophilia. On April 22, 60 per cent of 12,050 leukocytes were eosinophils, and the direct count was 1,139, increasing to 2,041 the next day. By April 25 there was increased but ill-defined, spotty infiltration, particularly in the middle third of the right lung.

On this day, 0.99 gm. of neoarsphenamine was injected and repeated three days later. Direct eosinophil count was 1,507 and leukocyte count was 12,500, with 13 per cent eosinophils on the day arsenic was begun. Gradual fall to normal occurred in the next two days. Appetite improved within one week after initiation of arsenic

therapy and conjunctivitis subsided in two weeks. Temperature became normal. On May 12 the patient was discharged to the family physician. At discharge, chest x-ray findings indicated clearing of infiltration, with residual thickening of the major interlobar fissures on the right. Symptoms were absent and physical findings normal. Urinalysis continued to reveal a small quantity of albumin and a few red blood cells and casts. Hemoglobin was 10.0 gm.; red blood cells, 3.62 million. A well

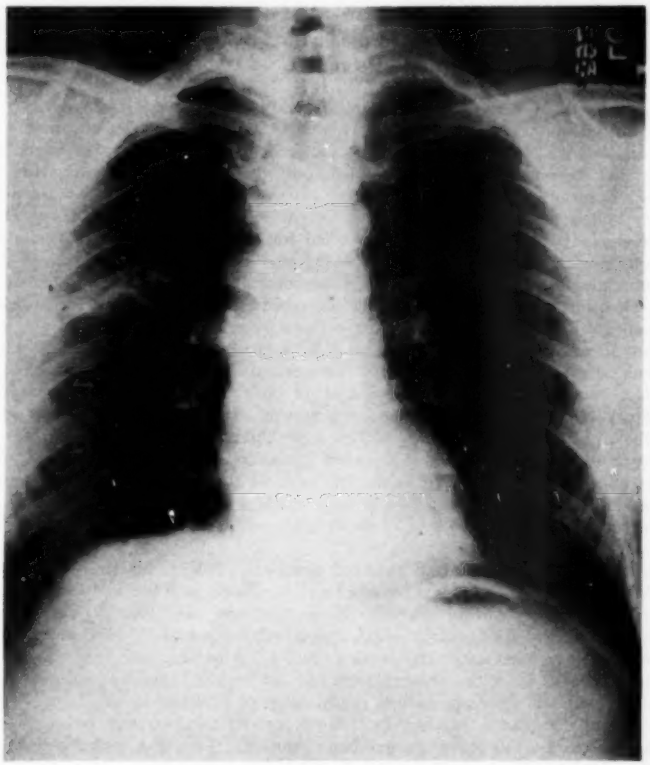

FIG. 10. *Case 3.* Chest roentgenogram after six days of ACTH, demonstrating clearing of infiltration.

balanced general diet with supplemental iron and vitamins was recommended. No other medications were prescribed.

When seen 17 days after discharge the patient had remained symptom-free; he had begun to gain weight and his anemia had improved. Urine was normal, as were plasma proteins in total and ratio. Nearly complete clearing of infiltration was observed in the chest x-ray. By June 23 the weight gain was 12 pounds. Symptoms were absent. Physical findings, hemogram and urine were normal. When patient

was last seen, in April, 1951, symptoms were absent; physical and roentgenographic findings were normal, and urine and complete blood count were normal.

Comment: More severe illness, albuminuria, casts, hematuria and altered plasma proteins, with a progressive downward course prior to treatment, suggest a more severe process than in cases 1 and 2. Presence of periarteritis nodosa is not excluded by a single negative muscle biopsy. Interruption of disease activity seemed to occur during administration of ACTH. Effectiveness of arsenicals is problematic, though it seemed to maintain remission begun after the first injection.

Case 4. A 64 year old white male farmer was admitted March 31, 1951. Dry cough, increasing weakness, weight loss, anorexia, malaise, moderate breathlessness, fever and headache had been increasing for four months. Illness was initiated with paroxysmal sneezing and dry cough, related, by the patient, to working with mouldy alfalfa. Exposure was discontinued after two weeks, and the sneezing subsided but the dry cough persisted. A 15 pound weight loss occurred in 90 days. Dyspnea and fever six weeks before admission called for the administration of penicillin and streptomycin. The family physician stated the chest roentgenogram was normal. No sulfonamides were administered. Generalized muscular aching, numbness and sharp, shooting pain in both hands and fronto-occipital headache had been present for one month. Past illness and allergic reactions were denied.

Admission examination revealed an elderly man with perspiring hot skin. There was evidence of recent weight loss. Temperature was 101.0° F. Multiple small, movable, nontender glands were palpable in both posterior cervical areas. Slight expiratory buzz was audible at the open mouth. Percussion was slightly impaired over the right midposterior chest. Râles were absent. Cardiac findings and electrocardiogram were normal. Blood pressure in the right arm, supine, was 140/60 mm. of Hg, and 144/62 mm. of Hg in the left arm. Pain, touch, temperature perception and muscle power were diminished in both hands and forearms. A small, nontender nodule was felt in the upper pole of an atrophic left testicle. Other physical findings were not abnormal.

Initial hemoglobin was 10.8 gm.; red blood cells, 3.01 million; sedimentation rate, 32 (Wintrobe) in one hour; hematocrit, 35. Blood non-protein nitrogen, sugar, albumin and globulin were normal. Kline test was negative, as were blood agglutinations for typhoid, paratyphoid A and B, tularemia and *Brucella abortus*. Blood cultures on three successive days were negative. Albumin, one plus, was present in an otherwise normal urine. Flocculation tests of hepatic function were not abnormal. Repeated sputa examinations did not reveal fungi or acid-fast bacilli. Stained sputum contained predominantly eosinophils. *Streptococcus viridans* and coagulase-positive *Staphylococcus aureus* were grown from sputum. The first leukocyte count was 12,650, with 69 per cent polymorphonuclears, 11 per cent lymphocytes and 20 per cent mature eosinophils.

Admission chest roentgenogram revealed bilateral, moderate hilar enlargement with increased linear markings. Nonconfluent infiltration in the right apex and above the right hilus had ill-defined borders. Infiltration was also visualized in the lower third of the left lung (figure 11).

Adequate parenteral doses of streptomycin and penicillin, with supportive measures including high calorie and protein diet and whole blood transfusions, did not alleviate symptoms or affect continued, spiking fever (chart 3). On April 4 the total leukocyte count was 14,250, with 57 per cent polymorphonuclears, 3 per cent basophils, 12 per cent lymphocytes, 6 per cent monocytes and 22 per cent mature

eosinophils. "L. E. cells" were not seen in sternal marrow, which contained an increased number of eosinophils and precursors in normal ratio. Roentgenographic abnormality was not demonstrated in skull, pelvis, spine or long bones. Spinal fluid dynamics, cell count and chemistry were not abnormal. Albuminuria, microscopic hematuria and 2 to 5 granular casts per high power field were present in repeated urinalyses. A progressive downward course was observed.

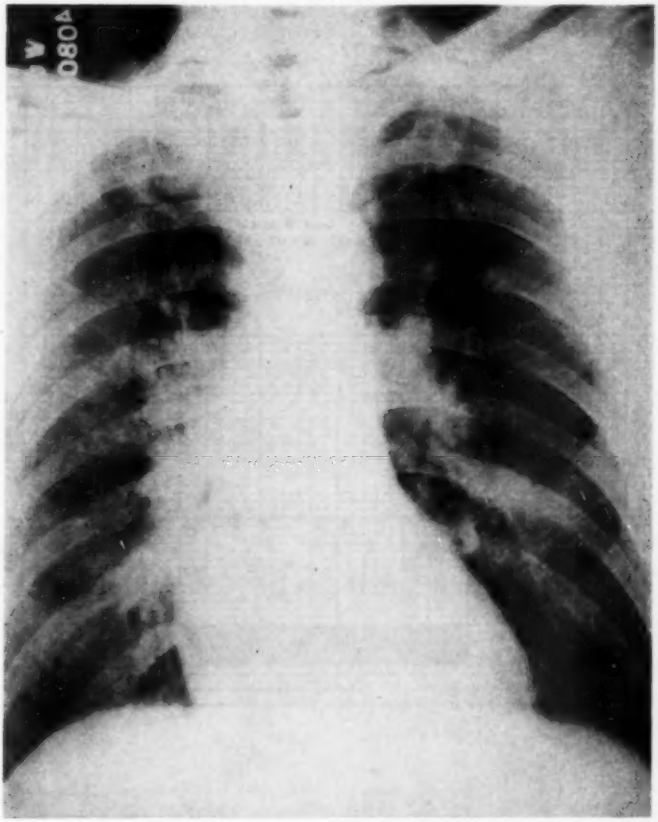

FIG. 11. *Case 4.* Admission chest roentgenogram. There is prominence of both hilar areas and non-confluent, patchy infiltration in mid left lung and right apex and near each hilum.

Clinical impression had been PIE syndrome. Primary or modifying diagnosis was proved when suspected periarteritis nodosa was demonstrated by microscopic examination of excised atrophic left testicle on April 17 (figure 12).

Cortisone, 100 mg. by hypodermal injection every eight hours, was begun on April 17. Temperature became normal within 12 hours. Cough and dyspnea grad-

ually subsided and appetite began to improve. Peripheral neuritis with weakness and extreme pain in both hands gradually improved during the next two weeks. Symptomatic mental depression, present on admission, was improved after two weeks of cortisone.

Direct eosinophil count of 2,019 the day before cortisone fell to 358 within 36 hours, and continued between 180 to 300 during hormone administration. Anemia and evidence of renal damage persisted.

Chest x-ray examination 36 hours after the first injection of cortisone demonstrated clearing of infiltration (figure 13). Four days later, continued resolution was

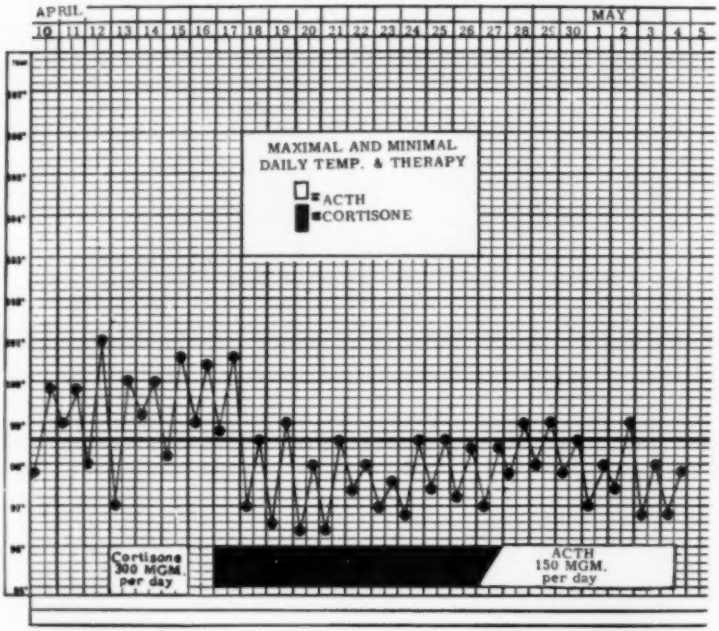

CHART 3. *Case 4.*

noted and this was maintained. Anemia continued and urinalysis was unchanged. Glycosuria was not present and blood chemistry remained near previous values. Blood pressure had elevated slowly to 180/100 mm. of Hg, and five pounds of weight had been gained.

On April 28 cortisone was gradually withdrawn and ACTH begun (25 mg. every four hours) since the direct eosinophil count had varied from 200 to 300. Continued clinical improvement was noted, and on May 1 chest roentgenogram evidenced little infiltration (figure 14).

On May 5 a cerebrovascular accident occurred and the patient died after five hours. In 18 days 3,350 mg. cortisone and 900 mg. ACTH had been given.

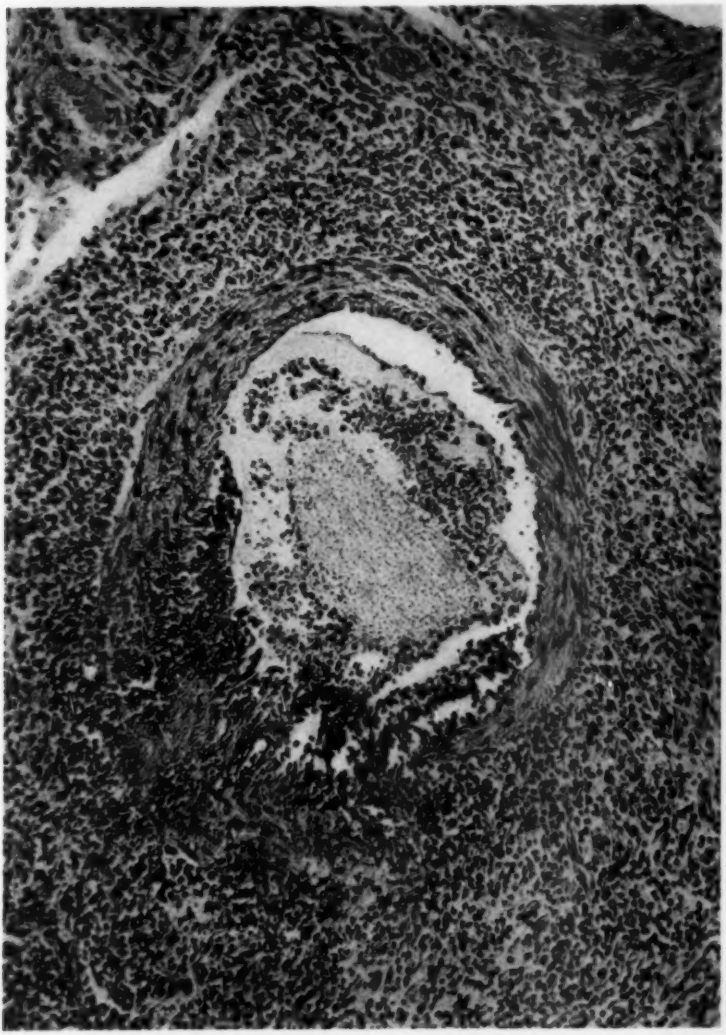

FIG. 12. *Case 4.* Photomicrograph of biopsy specimen (testicle). There are necrosis and extensive infiltration of arterial wall by polymorphonuclear and eosinophilic leukocytes. Extensive degeneration of endothelium with replacement by polymorphonuclear leukocytes and a few macrophages is seen. The arterial lumen contains a coagulum with enmeshed leukocytes. This picture is consistent with the diagnosis of periarteritis nodosa.

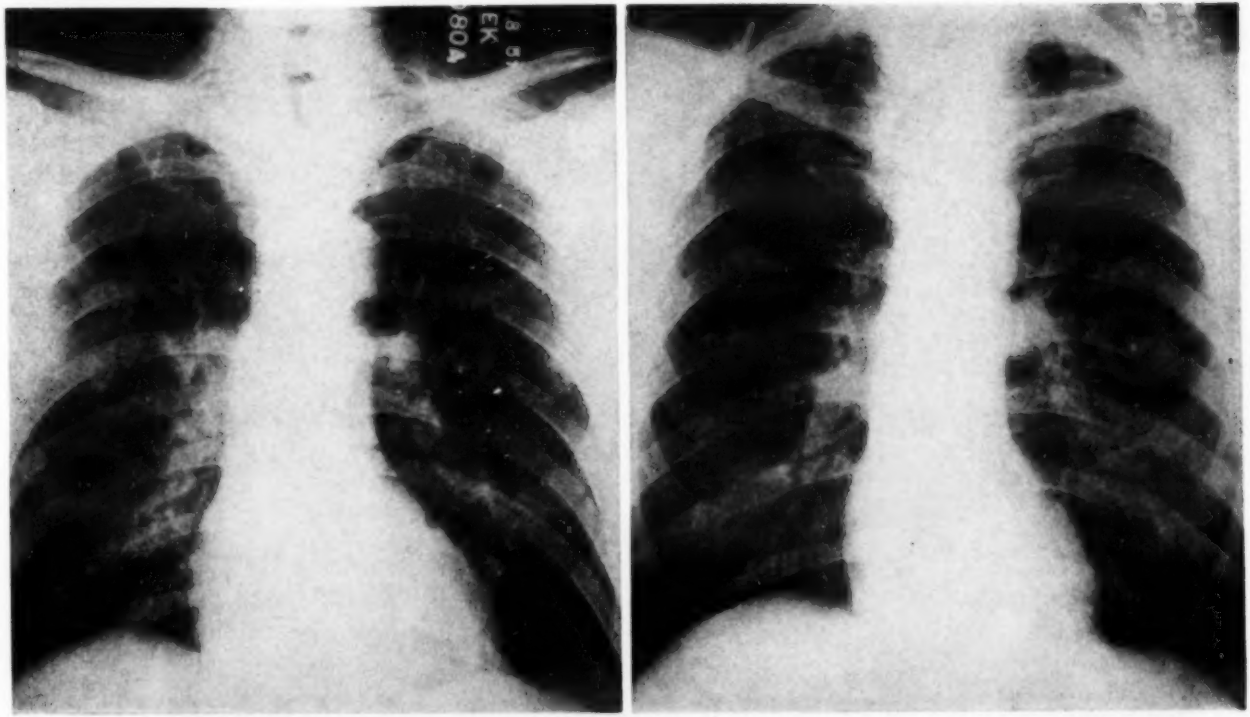

FIG. 13 (*left*). *Case 4.* Chest roentgenogram after 36 hours of cortisone. Infiltration is clearing.
FIG. 14 (*right*). *Case 4.* Chest roentgenogram after two weeks of ACTH and cortisone reveals no infiltration.

Postmortem examination revealed multiple small cortical abscesses of the kidneys. The lungs appeared normal. A large intracerebral hemorrhage was present in the right hemisphere. Microscopic examination revealed periarteritis in all organs, with variable degrees of fibrosis. There were no demonstrable microscopic evidences of periarteritis in pulmonary vessels, some of which contained thrombi.

Comment: Progressive periarteritis nodosa accompanied PIE syndrome in this case. Pulmonary infiltration present prior to steroid hormone therapy had cleared before the patient died. Periarterial eosinophilic infiltration was substantially less in autopsy sections than in biopsy specimen prior to therapy. Fatal cerebral hemorrhage has been previously attributed to periarteritis nodosa.[63]

Discussion

Many cases with PIE syndrome have been etiologically attributed to intestinal infestation and to bacterial and protozoal infection.[16-18] *Endamoeba histolytica* and *Endamoeba coli*,[19, 20] *Trichuris trichiura*,[21] cutaneous helminthiasis,[22] brucellosis,[23] coccidioidomycosis,[24-26] tuberculosis,[27] staphylococcus,[28] *Fasciola hepatica*,[29] microfilaria [30] and cheese mites [31] have been incriminated as causative. Thirty-one of 43 cases designated tropical eosinophilia had demonstrable parasitic infestation.[32]

Allergic bronchopneumonia was described in 1935,[33] and virtually all authors now attribute pulmonary infiltration with eosinophilia to an allergic reaction.[34] Stimulating, sensitizing and aggravating antigens vary, but the condition is often cast in the mold of an allergic past. History or present manifestations of hay fever, vasomotor rhinitis, eczema, migraine headache or urticaria were present in 51 cases in Loeffler's original series.[41] Fifty-two of Maier's [42] 100 cases had allergic symptoms. Pulmonary infiltration was observed in 11.6 per cent of 355 cases of bronchial asthma having routine chest roentgenograms.[43] Sixty-nine per cent of one series called Loeffler's syndrome had bronchial asthma [40] and 7 per cent had hay fever. The incidence of pulmonary infiltration with eosinophilia in bronchial asthma is 5 to 11 per cent, according to the same author,[40] and 5 to 8 per cent, according to another.[38] Many cases with associated bronchial asthma,[35, 39, 40, 44-52] angioneurotic edema [53, 54] and eczema [11] have been reported. Allergic skin reactions in PIE syndrome following administration of penicillin oil and wax have occurred.[54] Injection of a small quantity of staphylococcus vaccine was thought causative in one case.[55]

Antigen-antibody interaction liberates a histamine-like substance causing increased vascular permeability and resultant edema in affected tissue (shock organ).[56] Edema may be responsible for clinical manifestations of allergy.[57] The type of reaction following allergic insult depends upon such factors as the strength of the stimulant antigen, responsiveness of antibody production, and velocity and duration of the antigen-antibody reaction. Favorable or detrimental alteration of the reaction may result from previous antigenic exposure.[58] Consequent tissue injury may thus vary from transient and

reversible to necrotizing or granulomatous reactions of chronic course or fatal termination. States analogous to Loeffler's syndrome with complete reversibility have been produced by rendering rabbits allergic and observing the response by autopsies at regular intervals.[59] More profound sensitivity with greater allergic shock produced experimental lesions typical of periarteritis nodosa,[60] and the rôle of hypersensitivity in human cases of periarteritis has been asserted by Rich.[61, 62]

PIE syndrome may be a prominent presenting feature of periarteritis nodosa,[51] as was demonstrated in our case 4. Despite a recent report minimizing pulmonary involvement,[63] many others have emphasized pulmonary manifestations and have demonstrated involvement in nearly 28 per cent of cases of periarteritis coming to autopsy.[64-67] Associated allergic disease, especially bronchial asthma, has been recorded in 18 to 25 per cent of cases.[68, 69] Similar pathologic changes have been seen in polyarthritis rheumatica, Loeffler's syndrome, periarteritis nodosa and other allergic states, and Bergstrand [70] proposes that these conditions be appreciated as morphologic equivalents.

Postmortem examinations have been infrequent in PIE syndrome without associated lethal disease. The report of the pathologic findings in four cases after accidental death is most often cited.[71] One of four had an allergic background. Lobular and interstitial eosinophilic pneumonia without fibrin deposition was found with thrombosis of small interstitial vessels. Three cases with associated bronchial asthma evidenced similar eosinophilic pneumonia and thromboses with irregular areas of obstructive emphysema, edema and hyalinization of bronchiolar and bronchial basement membrane.[40] Analogous changes were recorded by Brock.[72]

Until recently, therapeutic measures, if any, have been directed toward symptomatic relief. Elimination of parasitic infestation seemed helpful [32] and modification of disease by epinephrine and aminophylline has been suggested.[26] Antibiotics, antihistamine drugs and histamine desensitization produced variable results.[8, 12, 13] Confirmation of Weingarten's observation of beneficial effects from arsenic in tropical eosinophilia soon occurred.[4, 8, 10, 13, 30, 31, 73-75] The effectiveness of arsenic may be attributed to its action as a cytoplasmic poison, with depression of total hematopoietic production or selective interference with eosinophil and other leukocyte formation.[76]

Following demonstration that pituitary adrenotrophic hormone lowers blood eosinophils in individuals with intact adrenals,[77-79] Rose [80] treated a case of Loeffler's syndrome with ACTH in 1947, reporting rapid fall in circulating eosinophils, radiographic clearing of pulmonary infiltration and alleviation of symptoms. Two small injections of the hormone lowered the eosinophil count without clinical or radiologic improvement in a case of tropical eosinophilia, and further ACTH was not given.[80] Similar experience with Loeffler's syndrome and tropical eosinophilia was again reported by the same author.[81]

Periarteritis nodosa has been previously treated with ACTH and cortisone, with clinical remission and reduction of eosinophilia during drug administration.[82, 83] Relapse following withdrawal of steroid therapy was usual.

Many cases of PIE syndrome are asymptomatic and of mild and transient nature, and seem produced by reversible tissue reaction. When more severe damage results in symptomatic chronicity and progression, concentrated therapeutic effort is indicated. Ultimate recovery may be enhanced by early diagnosis and prompt institution of therapy. Reversibility of the process may be possible early in the disease. Credence of possible reversibility is enhanced by reports of periarteritis proved by biopsy with ultimate apparent "recovery."[67]

Summary and Conclusions

1. Literature pertaining to Loeffler's syndrome, tropical eosinophilia and related conditions has been reviewed.

2. Pulmonary infiltration with eosinophilia (PIE syndrome) may accompany allergic diseases of variable severity.

3. Cases illustrating reversible, prolonged and fatal outcome are presented.

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CHOLANGIOLITIC BILIARY CIRRHOSIS (PRIMARY BILIARY CIRRHOSIS) *

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Among the various forms of biliary cirrhosis a clinicopathologic entity can be segregated in which there is no obstruction or inflammation in the extrahepatic or larger intrahepatic biliary ducts or gall-bladder. Histologically, the main lesion consists of an inflammation in and around the smaller bile ducts (Hering's canals or junction ducts), or in the canaliculi between the lobules, or both. The term cholangioles has been broadly used [1] to include both the finer biliary radicles and the bile canaliculi, and the term cholangiolitic cirrhosis for the inflammation of these areas.[1] Rössle [2] has restricted the term cholangitic biliary cirrhosis to ascending cholangitis involving the extrahepatic as well as the intrahepatic biliary tract, usually associated with incomplete obstruction. Some other synonyms for cholangiolitic biliary cirrhosis are pericholangiolitic biliary cirrhosis,[3] cholangiolitic biliary cirrhosis,[2] chronic intrahepatic obliterating cholangitis,[4] nonobstructive cholangitic biliary cirrhosis,[5] intrahepatic cholangitic biliary cirrhosis,[6] Hanot's biliary cirrhosis, and cholangitis lenta.[7, 8]

Since there is a great deal of controversy about this form of biliary cirrhosis, the observations made on nine cases seem worthy of report and analysis. These cases are described separately and then analyzed with respect to clinical, functional, electrophoretic and pathologic findings.

Methods

Specimens used in testing liver function were obtained simultaneously, and determinations were made as previously reported.[9] The electrophoretic separation of the serum proteins was performed with standard apparatus and technic, the experimental details having been given in a previous report.[10] The liver sections obtained from surgical and punch biopsies and also from necropsy material were fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin, hematoxylin-eosin-azure (Maximow's stain), Mallory-azan for connective tissue and silver stain for reticulin. In some cases, frozen sections were stained with Sudan IV to demonstrate neutral fat.

Case Reports

Case 1. A white married female, 27 years old when her illness began early in 1942, had no significant family history. While in college, at the age of 18, she had

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drunk whisky (as many as eight to 10 shots daily) and beer (12 or 14 glasses daily). This habit persisted until the onset of her present illness. The first symptom she noticed was itching on the soles of her feet; otherwise, she felt well. In July, 1942, she developed jaundice. A local physician administered a high fat diet and bile salts in tablet form, which were followed by more intensive itching; by the end of August,

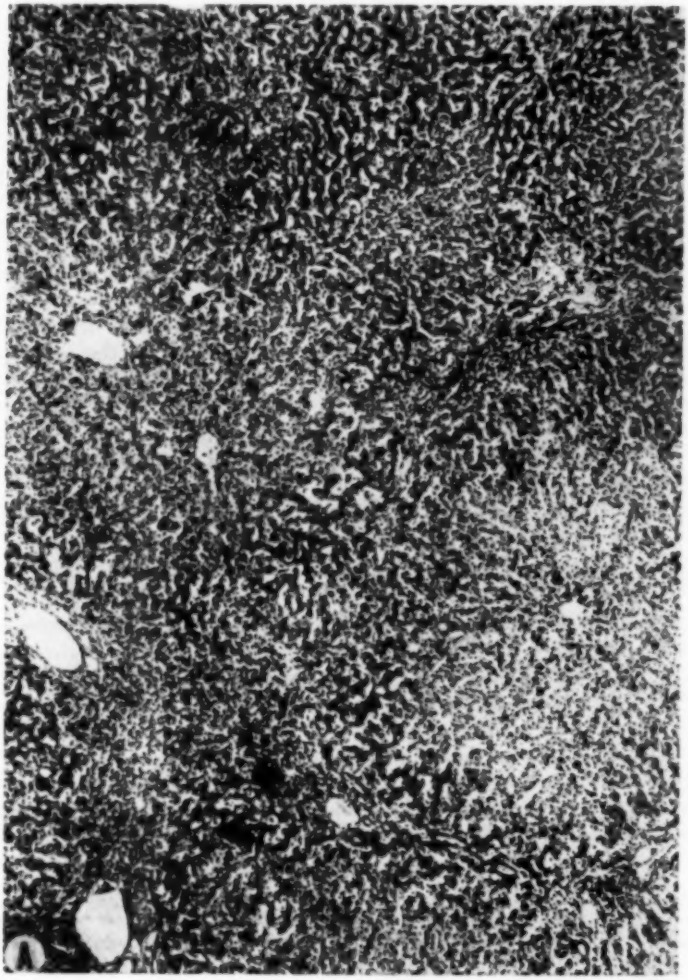

FIG. 1*A*. *Case 1.* Low power view of surgical liver biopsy, taken about 10 months after onset of symptoms. Note the increase of cells in the periportal areas but with normal architecture preserved.

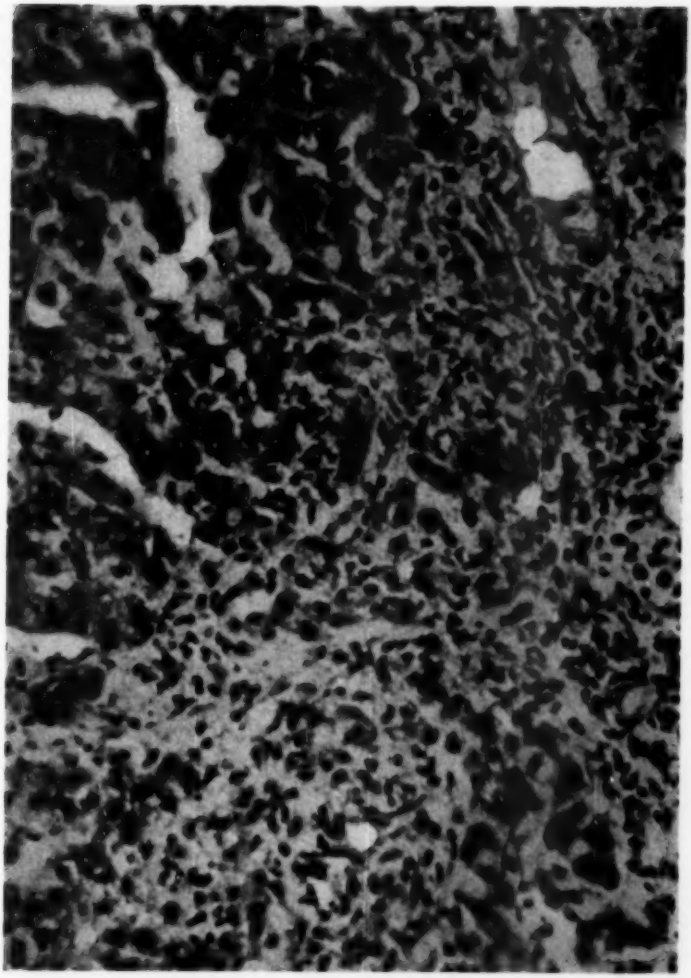

FIG. 1*B*. *Case 1.* High power view of same biopsy as figure 1A, showing intense infiltration of leukocytes, many of them polymorphonuclear, at the edge of a portal triad. The absence of identifiable small bile ducts is apparent.

this had become unbearable despite barbituric sedation. On November 3, 1942, she was hospitalized in Denver, Colorado, and on November 14 an exploratory laparotomy was performed. No gross lesion was found in the bile ducts or the gall-bladder. The liver edge was approximately two inches below the costal border. The liver had a greenish color with a smooth surface. The gastrohepatic ligament was thickened,

and large glands the size of the distal joint of the thumb were found to extend down behind the duodenum. The pancreas had a normal appearance. The extrahepatic bile ducts were free of obstruction or gross evidence of inflammation. A T-tube was inserted in the common bile duct and a biopsy of the liver was taken.

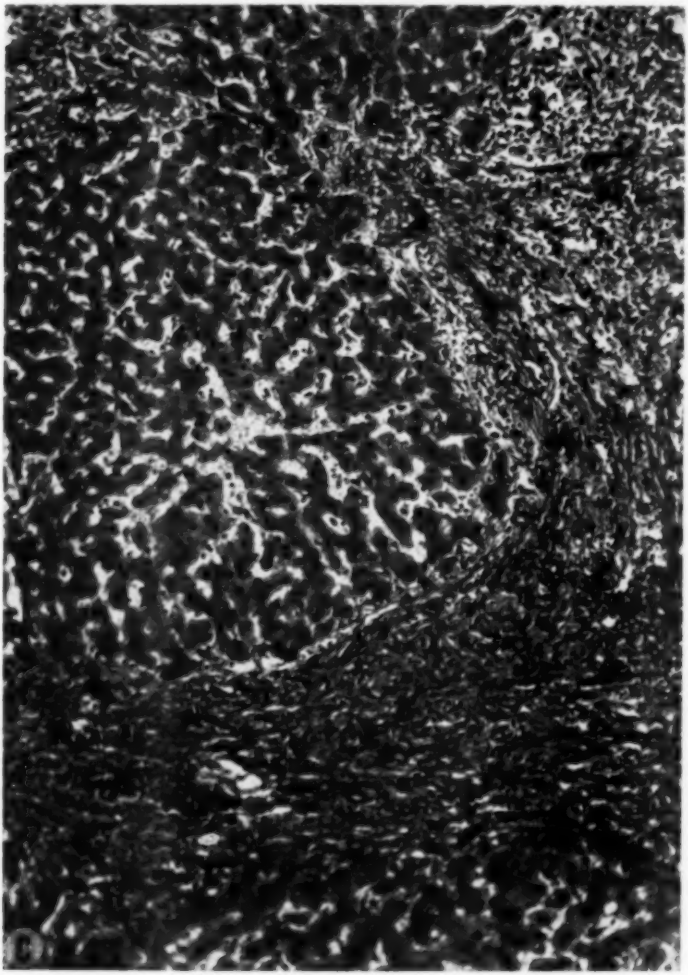

FIG. 1C. *Case 1.* Low power view of surgical biopsy of the liver, removed about nine years after the onset of symptoms and about one year after a "spontaneous" decrease of hyperlipemia, jaundice and xanthomas. The liver now shows large collagen bands separating a normal appearing liver parenchyma, giving an appearance similar to portal cirrhosis.

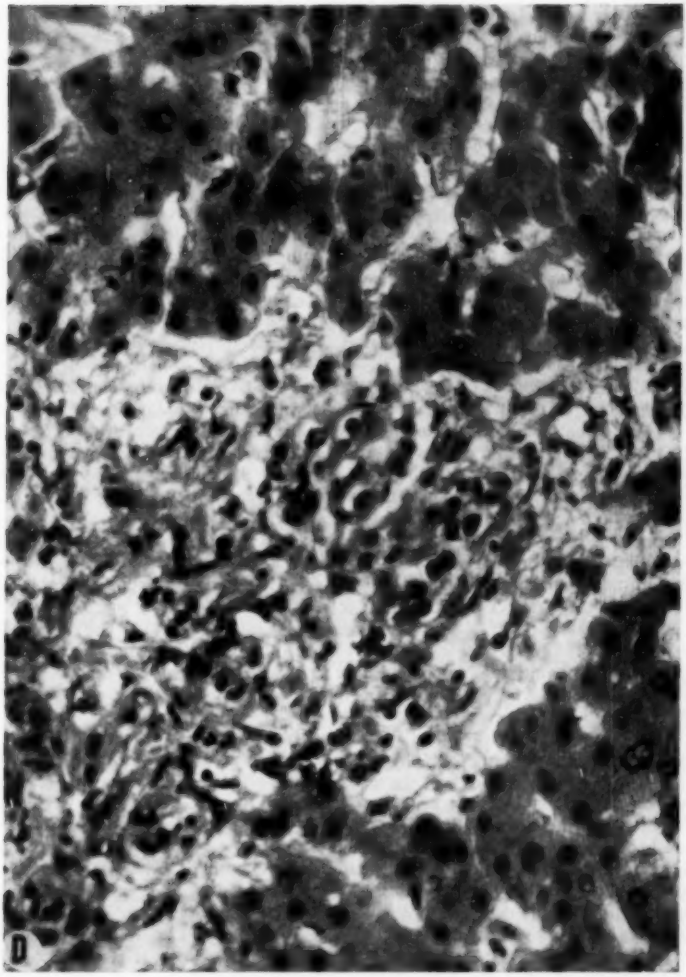

FIG. 1*D*. *Case 1.* High power photomicrograph of the same section as figure 1C, showing the dense collagenous tissue with only a few inflammatory cells. Small bile ducts are not visible. The parenchymal cells show a normal cord pattern and no evidence of degeneration.

A marked broadening of the portal tracts was seen, with minimal fibrosis and a marked cellular infiltrate around the smaller bile ducts, which had proliferated. The type of cell seen in the triads varied; polymorphonuclears, mononuclears and fibroblasts were among the most common (figure 1, A and B). The cords were well pre-

served, with a generalized infiltrate of mononuclear cells. The parenchyma disclosed no degenerative features or fatty infiltration. No xanthoma cells were present. The larger bile ducts showed no dilatation or alteration of their structure. The impression was that of a biliary cirrhosis with inflammation in and around the smaller bile canaliculi.

A maximum of 250 c.c. of bile per day, with a daily average of 200 c.c., was obtained from the T-tube drain. During the following weeks it was observed that the jaundice decreased and that the patient felt no itching. She was discharged from the hospital on December 16, 1942. One month later she again noticed generalized itching, and for the first time noticed yellow streaks in the creases of the palms of her hands and xanthelasma of the eyes. On the advice of a friend she drank a quart of carrot juice daily for almost a month, but this was discontinued when no change was observed in the course of the disease. The T-tube had stopped draining bile, and there was inflammation of the skin around the tube. The patient came to this institution for the first time on April 16, 1943.

At physical examination, she appeared a moderately jaundiced young adult white female, of dark complexion, without signs of acute illness. She was well nourished, athletically built and coöperative. Blood pressure and pulse were normal. Because of the presence of the draining T-tube in the right upper quadrant, the liver could not be well palpated but was thought to be enlarged. Splenomegaly was present, as well as xanthelasma of the eyelids and xanthoma streaks in the creases of the palms, with darkening of the skin without pigmentation of the mucosae. The remainder of the physical examination was essentially negative. Laboratory data reported bile in the urine but were normal otherwise. There were 17,600 leukocytes and 4.4 million erythrocytes per cu. mm., and 13.2 gm. per cent of hemoglobin. The differential count indicated 69 per cent polymorphonuclears, 23 lymphocytes, 5 monocytes and 3 eosinophils. The Kahn reaction was negative. The serum bilirubin direct was 3.5 mg. per cent, the total 5.1 mg. per cent; total cholesterol was 550 mg. per cent, with 275 mg. per cent esters; total lipids were 3,110 mg. per cent. The total plasma proteins were 7.33 gm. per cent, with 2.24 albumin and 3.09 globulin. Repeated lipid determinations a month later indicated total lipids of 2,925 mg. per cent, phospholipid, 1,255 mg. per cent; total cholesterol, 910 mg. per cent, with 180 mg. per cent esters; neutral fat, 630 mg. per cent.

The T-tube was removed and the patient placed on a low fat diet (2 to 4 gm. daily), with 250 to 400 gm. carbohydrates and 50 to 100 gm. proteins daily. With this diet, no consistent changes in the serum lipids or in the course of the disease were observed. Two hundred sixty grams of lipocaic were given daily for a period of 10 days without producing any notable change. An electrophoretic separation of the serum proteins indicated a marked increase in the beta and gamma globulin fractions (table 1). The patient was discharged on June 2 with the disease essentially unchanged. Two months later the patient became pregnant, and with pregnancy she noticed a considerable decrease in the jaundice as well as a fall in lipid values. On November 30, the direct reacting bilirubin was 1.4 mg. per cent, the total bilirubin 2.3 mg. per cent; the total cholesterol had dropped to 286 mg. per cent, with 149 mg. per cent esters; and the total lipids were 1,425 mg. per cent.

In the third month of pregnancy the patient had a miscarriage. She continued in fairly good condition until February, 1944, when she again noticed an increase in the jaundice, and a considerable rise in lipids was detected. The direct reacting bilirubin was 7.1 mg. per cent, the total 9.2 mg. per cent; total cholesterol was 584 mg. per cent, with 292 mg. per cent esters; total lipids were 2,777 mg. per cent. In April she was given 30 c.c. of progesterone daily. With this treatment she seemed to improve slowly, but there were no significant changes in the circulating lipids. On December 9 the direct reacting bilirubin was 5.4 mg. per cent, with total bilirubin 8.4

mg. per cent. The total cholesterol was 2,050 mg. per cent, with 995 mg. per cent esters and the total lipids had risen to 6,745 mg. per cent. The total proteins were 7.56 gm., with 4.18 gm. albumin and 3.38 gm. globulin. The degree of xanthomatosis was more apparent in February, 1945, when she was last seen in this institution. Her course remained unaltered during the following months. Since 1946 she has been under observation at the hospital of the Rockefeller Institute in New York.[11] She did poorly in 1946 and 1947 and became embarrassed about her personal appearance, the xanthomata having grown to enormous size. She was unable to use her hands because of the swelling of the palms as a result of the xanthomatous lesions, and she spent most of her time in seclusion in Denver and Florida. In February, 1948, it was found that the total lipids were 2,500 mg. per cent, the total cholesterol 833 mg. per cent, phospholipids, 1,395 mg. per cent. Serum bilirubin was 1.7 mg. per cent direct and 3.6 mg. per cent total. Total proteins were 8.90 gm., with 4.15 gm. albumin and 4.75 gm. globulin. Thymol turbidity was 21 units, zinc turbidity 25 units, and alkaline phosphatase 34 units.

TABLE I

Cholangiolitic Biliary Cirrhosis

Subject	Time after Onset of Jaundice	Plasma Proteins gm. per cent	Electrophoretic Data										
			Per Cent					Gm. per Cent					
			Alb.	α1	α2	β	γ	Alb.	α1	α2	β	γ	A/G
B. J.	2½ yrs.	7.99	41.1	6.0	12.8	27.1	13.0	3.28	4.8	1.02	2.17	1.04	0.69
Z. M.	3 wks.	8.82	30.6	6.9	13.2	11.8	37.5	2.70	0.61	1.12	1.04	3.31	0.44
R. W.	6 yrs.	7.57	50.5	9.6	13.1	18.2	8.6	3.82	0.73	.99	1.38	.65	1.02
M. B.	8 mos.	7.56	27.4	5.2	13.2	37.4	16.8	2.07	0.39	.99	2.82	1.29	0.38
Normal Sera													
Average		7.01	60.3	4.0	9.7	12.8	13.2	4.23	0.28	0.68	0.89	0.93	1.52
Standard deviation		0.30	2.8	0.8	1.5	1.2	1.7	0.29	0.06	0.10	0.08	0.13	0.18

In the spring of 1949, the patient suffered gastrointestinal bleeding due to esophageal varices. It was also noticed at that time that there was a considerable change in the course of her illness; the jaundice decreased and finally disappeared, and there was a considerable drop in the total cholesterol values in the sera. The xanthomata in the skin rapidly regressed. On May 9, 1949, an anastomosis of the portal vein to the caval vein was performed.[12] The liver was then found to be quite enlarged and firm in consistency, its surface finely granular and fibrotic. The spleen was enlarged to twice its normal size. No stones or dilatation were observed in the biliary tract. An initial portal vein pressure of 440 cm. of water dropped to 205 cm. of water after the shunt.

Histologic examination of the biopsy removed on May 9 showed the liver to be divided into irregular areas of relatively normal-appearing parenchymal cells by well demarcated, narrow and dense strands of connective tissue. The segregated nodules were not lobular in distribution and varied from one-half to three lobules in size. Bile ducts were not seen in either the relatively normal portal triads or in the proliferated fibrous tissue, nor was there any evidence of bile duct proliferation. On the other hand, there was no evidence of dilatation of bile canaliculi or bile pigment stasis in the canaliculi, hepatic cells or Kupffer cells. The fibrous tissue strands contained occasional lymphocytes. No xanthoma cells were seen. The parenchymal

cells showed no evidence of degenerative change. The cord pattern was preserved and the cytoplasm was uniform and finely granular. The parenchymal cell nuclei were uniform and showed no evidence of recent proliferation. The triadal and central vascular elements were not remarkable. The impression was that of a marked unilobular and multilobular cirrhosis, with little proliferation of the bile ducts and minimal inflammatory activity.

Case 2. A 36 year old Spanish housewife was admitted to the clinic for the second time on June 30, 1950. She had been treated here in 1942 for Raynaud's disease. At that time she had a bilateral cervicothoracic sympathectomy, following which the ulceration and pain in the fingers disappeared. She had no other pertinent past or familial history.

The patient referred her present illness to January, 1949, when she had suffered from an infected wisdom tooth. She had suddenly become jaundiced and had remained in that condition until the time of her present admission. She did not complain of pain in the right upper quadrant, chills or fever, but since the onset of jaundice had suffered from pruritus, dark urine and occasionally acholic stools. Her appetite remained fairly good, but she felt weak and tired. Two months before admission (14 months after the onset of jaundice) she noticed appearance of small yellow plaques on her eyelids. Her menstrual periods became prolonged after October, 1949, with profuse bleeding continuing for as much as 10 days each time.

On admission to the hospital on June 30, 1950, she was a slightly built, not acutely ill woman of dark complexion. The skin was quite dark and markedly icteric. Xanthelasma was evident in patches on the eyelids bilaterally. Pulse and blood pressure were within normal range. The liver was firm and smooth, extending 5 to 6 cm. below the costal border in the midclavicular line; the spleen was palpable 2 cm. below the costal margin. The remainder of the physical examination was essentially normal.

Laboratory data indicated a normal urine, except for the presence of bile. The counts were as follows: leukocytes, 12,800; hemoglobin, 10.7 gm.; erythrocytes, 3.8 million per cu. mm.; differential count, normal. The Kahn reaction was negative. The CO_2, pH and chloride values were normal. Roentgenograms revealed nonvisualization of the gall-bladder. No radiopaque calculi were visualized in this region. Liver tests gave the following results: direct reacting bilirubin, 7.8 mg. per cent, with a total bilirubin of 8.8 mg.; total cholesterol, 580 mg. per cent, with 150 mg. esters; total lipid, 2,200 mg. per cent. The total plasma proteins were 7.6 gm., with 4.1 gm. albumin and 3.5 gm. globulin; prothrombin time was 100 per cent of normal; alkaline phosphatase, 40.5 units; cephalin cholesterol flocculation, plus 4, and the thymol turbidity, 9 units. Urobilinogen on a 24-hour specimen was .7 mg.; fecal urobilinogen was 8.5 mg.

Laparotomy was advised but the patient refused. She was discharged on July 14, and her clinical course elsewhere has remained unchanged for a subsequent period of eight months.

Case 3 (table 2, figure 2A). A 51 year old white housewife had had rheumatoid arthritis for 10 years (since 1938), with swelling of all the joints of the extremities and of the neck and jaw, and a chronic productive cough. Various types of medication, among which was a course of gold therapy a month before admission, did not significantly alter the course of the disease. She had had a progressive loss of weight of approximately 15 pounds during 1947. The past history was otherwise noncontributory, and no significant familial history was detected. At the time of admission, on May 29, 1948, she appeared chronically ill, abnormal findings being restricted to the joints. There was moderate swelling of the wrist joints, plus a variable degree of tenderness and limitation of motion of the proximal interphalangeal joints of all fingers. The urine was normal. Blood counts showed 5,200 leukocytes and 4.0

million erythrocytes per cu. mm., and 12.6 gm. per cent of hemoglobin. The corrected sedimentation rate was 50 mm. The Kahn test was negative. Roentgenograms of the chest indicated emphysema of the lungs and bronchiectasis in the left upper lobe, with compensatory dilatation of the structure of the upper lobule. The esophagus, stomach, duodenum and colon were essentially normal.

The patient was confined to bed and maintained on a palliative treatment of aspirin, barbiturates and codeine. On June 2 she suddenly became jaundiced, and her condition became increasingly severe in the following days. The liver and spleen were not enlarged but there was some tenderness on deep palpation in the right upper quadrant. There were no chills but her temperature oscillated between 37 and 38.5° C. The urine contained bile but was otherwise normal. A series of liver studies, done two days after the onset of jaundice, disclosed surprising findings, as indicated in table 2, with high values of total cholesterol, bilirubin and alkaline phosphatase, marked abnormality of the cephalin tests, and normal prothrombin time, hippuric acid excretion and urinary urobilinogen. A punch liver biopsy taken on June 18 revealed striking changes in the smaller bile ducts of the liver.

TABLE II

Tests of Hepatic Function in Course of Case 3 with Cholangiolitic Biliary Cirrhosis

Follow-up	Bilirubin mg. per cent		Cholesterol mg. per cent		Protein gm. per cent			Alkaline Phosphatase Units	Cephalin-Cholesterol Flocculation	Thymol Turbidity Units	Hippuric Acid Grams	Urobilinogen mg. per 24 hours		Prothrombin Time per cent
	Direct	Total	Total	Esters	Albumin	Globulin	Total					Urinary	Fecal	
6– 4–48	1.7	2.3	530	180	3.59	5.47	9.06	44.8	4+	>20	1.0	.67	8.55	96
6–15–48	2.8	3.6	410	195	3.71	5.11	8.82	57.5	4+	>20	1.0	—	—	—
6–28–48	6.3	10.3	420	92	3.45	5.29	8.74	46.8	4+	>20	1.0	—	—	—
7–12–48	5.5	7.1	335	105	3.16	5.72	8.88	50.8	4+	>20	1.0	—	—	100
8– 6–48	7.5	10.2	420	108	2.85	5.52	8.47	49.3	4+	>20	1.2	—	—	—
9–14–48	4.2	5.8	430	113	2.78	5.70	8.48	52.7	4+	>20	1.1	—	—	72
3–21–49	3.0	3.9	228	103	2.88	3.27	6.15	45.7	4+	>20	.7	—	—	88
2–14–50	2.0	2.5	210	115	3.47	3.55	7.02	40.0	4+	>20	—	—	—	90

This biopsy showed four portal triads. All of them revealed disappearance of small bile ducts and a moderate inflammatory infiltration by lymphocytes, polymorphonuclear leukocytes and a few plasma cells. No xanthoma cells were seen. There was only slight increase in fibrous tissue and no intralobular fibrosis. There was no evidence of proliferation of bile ducts. The parenchymal pattern was normal and the cells showed no evidence of degenerative changes, although many contained yellow-green pigment. No inspissated bile was seen in canaliculi, although occasional small foci of inflammatory cells in the lobule might be interpreted as cholangiolitis. There was no evidence of degenerative or necrobiotic changes in liver cells, and a section stained with Sudan IV failed to reveal fatty change. No vascular abnormalities were seen.

The patient continued to have jaundice and also suffered from gingival bleeding and itching of the skin. The pain in the joints decreased considerably. During the following weeks the jaundice remained, varying in intensity from 3 to 10.2 mg. per cent total bilirubin, and the alkaline phosphatase remained elevated. Penicillin administered in doses of 300,000 units daily for 15 days did not change the course of the disease. She was discharged on September 14, still jaundiced but in fairly good

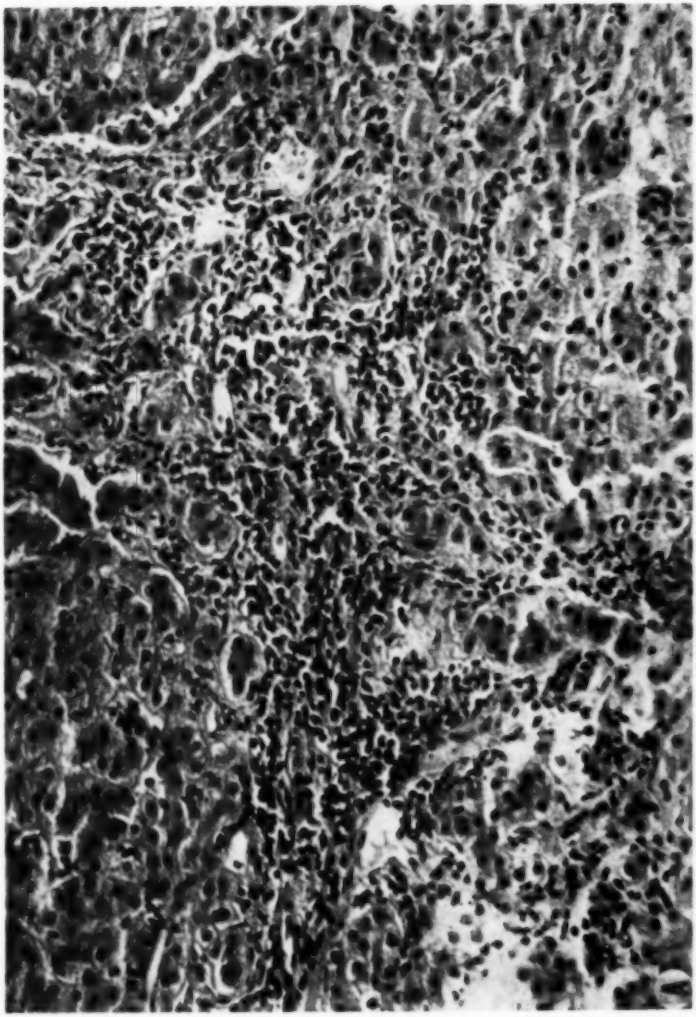

FIG. 24. *Case 3.* Section of liver removed at surgical biopsy about 16 days after the onset of jaundice. Note the intralobular inflammation along the course of bile canaliculi, with well preserved parenchymal cells in adjacent areas.

condition and with minimal joint difficulty. She remained in much the same condition until March, 1949, when she was seen again. The findings were similar, except that at this time the liver was firm and enlarged 3 to 4 cm. below the costal margin. The hepatomegaly was progressively increasing in size, reaching 7 to 8 cm. below the costal margin in the midclavicular line by March, 1950. There was no noticeable splenomegaly. The jaundice persisted, as did the chronic cough. There had been several episodes of exacerbation of joint pain. The liver tests disclosed, as the only significant change, a fall in the degree of cholesteremia to 210 mg. with 115 mg. esters.

Case 4 (figure 2B). A 10 year old boy, first admitted on January 2, 1943, had developed diarrhea two years previously, with as many as 10 to 12 loose bloody stools daily. He felt weak, tired and feverish. All the symptoms except the diarrhea subsided in about 10 days, but the diarrhea persisted with intermittent exacerbations and remissions. After proctoscopy, a diagnosis of chronic nonspecific ulcerative colitis was made. It had already been noticed in 1942 that the spleen was enlarged, producing a distressing sensation of pressure in the left upper quadrant of the abdomen and forcing curtailment of physical activities. He had suffered a progressive loss of nearly 30 pounds in weight. On admission, he appeared undernourished, without apparent acute illness. A slight jaundice was noticeable, especially in the sclerae. The most important findings were confined to the abdomen. There was extensive, uniform enlargement of the liver which was firm and nontender and extended 5 to 6 cm. below the costal margin. The spleen likewise was markedly enlarged, extending at least 8 cm. below the costal margin and appearing quite firm. Proctoscopy showed a granular, friable, bleeding mucosa, with the characteristic appearance of chronic nonspecific ulcerative colitis. Laboratory data were as follows: Urine was normal, except for the presence of bile; blood counts indicated 6,500 leukocytes and 4.76 million erythrocytes per cu. mm., and 13.5 gm. per cent of hemoglobin; differential count showed 74 polymorphonuclears, 26 lymphocytes and 10 monocytes. A glucose tolerance test was normal. The total bilirubin values were 2.2 mg. per cent. Fragility test was normal. The total plasma proteins were 6.3 gm., with 4.3 gm. of albumin and 2.0 gm. of globulin. Stool examinations were positive for blood using the benzidine test, but negative for parasites on several occasions. Roentgenograms indicated a normal esophagus, stomach and duodenal bulb, no shortening of the colon was evident, and no typical pattern of ulcerative colitis.

On April 12 an exploratory laparotomy was done. The liver appeared quite firm, with a slightly irregular surface; it was biopsied. The spleen was removed and found to weigh 466 gm.; its surface was purplish-red and smooth, offering increased resistance to cutting. No lesion was revealed in the gall-bladder or the extrahepatic biliary tract. The histologic findings were as follows:

The portal triads were enlarged, mostly by early fibroplasia, proliferating small bile ducts and infiltrating leukocytes. Some of the increased fibrous tissue was quite dense and collagenous. In some areas, slender bridges of collagen connected adjacent triads. Many of the preëxisting small bile ducts showed acute necrosis of epithelium and invasion by polymorphonuclear leukocytes. There was no dilatation of or bile pigment in the larger bile ducts. The diffuse triadal inflammatory cellular response was made up almost equally of polymorphonuclear leukocytes and lymphocytes. Slender fingers of new bile ducts supported by a delicate stroma extended into the lobules in a few areas. In general, however, the lobular architecture was preserved, and there was no evidence of inspissated bile in canaliculi, nor was there evident bile pigment in liver cord cells or Kupffer cells. Occasional parenchymal cell nuclei were pyknotic, and the cytoplasm of a few cells was deep red and hyalinized; but most of the cells were uniform and showed no evidence of degeneration or regeneration. Several of the lobular central veins were ringed by polymorphonuclear leukocytes, but no other vascular change was seen.

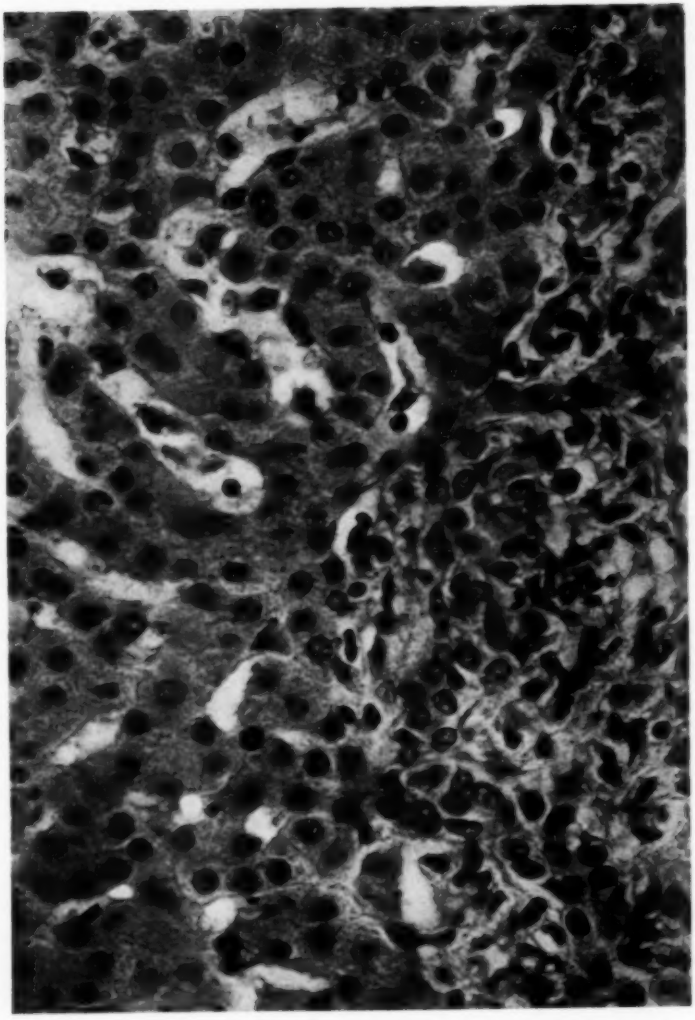

FIG. 2B. *Case 4.* High magnification of liver biopsy several months after the onset of jaundice. Note the immature small bile ducts without lumens. The adjacent cords of parenchymal cells show remarkable preservation.

Histologic examination of the spleen disclosed marked congestion, dilatation of the blood sinuses and increase in cells throughout the red pulp. There were marked hyperplasia of the reticulum and increase in the blood-forming tissue. Some vessels revealed hyalinization. Eosinophils and polymorphonuclears were scattered throughout the section.

The postoperative course was uneventful. The patient was discharged on a bland diet and followed at irregular intervals in the Outpatient Department. During the following months he got along fairly well, maintaining adequate nutrition and carrying on a fairly normal existence except for the restriction of physical exertion. There were occasional exacerbations of diarrhea, abdominal cramps and pain, but throughout most of this period there were only two to three loose bowel movements daily.

On April 2, 1944, the patient developed a high fever (about 102° F.) and erythematous patches on the skin of the arms and legs (erythema nodosum), some of which became ulcerated and suppurated (pyoderma gangrenosum). He was hospitalized, kept in bed and given a course of sulfadiazine therapy, with a dose of 2 gm. daily for 31 days, together with the application of sulfathiazole ointment to the skin. The skin lesions healed slowly, leaving definite scars, and the fever disappeared. There was no exacerbation of diarrhea during this episode, and the patient was discharged, markedly improved, on May 5, 1944. During the following three years he remained in good general condition, stools averaging two to three daily. On December 25, 1947, he suddenly developed a fever of 39.6° C., with chills and anorexia; his pulse was 120, blood pressure 110/70 mm. of Hg. He appeared pale, thin, undernourished and slightly jaundiced, and seemed both acutely and chronically ill. The liver remained as before, markedly enlarged, 7 to 8 cm. below the costal margin, the edge being quite sharp. Other physical findings were essentially normal. With bedrest, sulfadiazine and penicillin therapy, the fever subsided within four days. The urine was normal except for traces of bile. Blood counts disclosed 17,600 leukocytes, 4.2 million erythrocytes, and 10.2 gm. per cent of hemoglobin; the differential count was 86 per cent polymorphonuclears, 13 lymphocytes and 1 monocyte. The stools were 1 to 4 plus positive for blood by the benzidine test. Total plasma proteins were 6.75 gm., with 3.38 gm. albumin and 3.37 gm. globulin; alkaline phosphatase was 16.9 units; direct reacting bilirubin in the sera, 3.1 mg. per cent, with a total bilirubin of 4.3 mg. The prothrombin time was 100 per cent of normal; intravenous hippuric acid elimination, .8 gm.; thymol turbidity, 8.8 units, and cephalin cholesterol flocculation, plus 1. A quantitative urobilinogen determination in 24-hour specimens indicated .13 mg. in the urine.

These sections showed a marked increase of the degree of fibrosis about the portal triads, with little evident distortion of the lobular architecture. Larger triadal bile ducts were only rarely seen and were collapsed, but there were many apparently newly formed small bile ducts at the periphery of each triad. These appeared compressed, with little or no visible lumina. Many of them were surrounded by numerous bizarre-shaped hepatic cells. Occasional canaliculi containing inspissated green pigment were seen. Otherwise, the parenchyma was not significantly altered. The sections did not allow adequate evaluation of the degree of fibrosis between adjacent triads.

During hospitalization, stools remained semi-formed, with only one bowel movement daily. Proctoscopic examination disclosed minimal granularity of the mucosa, without friability or bleeding. After his discharge, the patient was seen again on December 1, 1949. He has remained in excellent physical condition and is at present a university student. The mucosa of the rectum reveals a normal aspect, except for slight atrophy. The liver has not changed in size; functional tests indicated a change only in a decreased alkaline phosphatase to a level of 8.8 units. On December 21,

1949, electrophoretic separation of the serum proteins revealed the persistence of a characteristic peak of beta globulin.

Case 5 (figure 3). A 63 year old housewife was known to have had essential hypertension for 16 years. In 1946 she suffered a "stroke," with apparently a transitory hemiparesis. Her present illness began in September, 1949, when the skin became slightly yellow and then definitely icteric, with a progressive darkening of the urine and clay-colored stools. In December, 1949, the patient first noticed itching of the skin and had suffered a progressive weight loss amounting to 45 pounds by the time of her admission to the hospital on April 22, 1950. Pruritus at times was so intense that it kept her from sleeping, bringing on fits of depression and a wish for suicide. Her past and familial history was otherwise noncontributory. She had never drunk alcoholic beverages.

Physical examination disclosed a well developed but emaciated woman, markedly icteric and appearing much older than her stated age. She was not in acute distress, but scratch marks were apparent over her entire body. Her blood pressure was 190/88 mm. of Hg. There was a slight enlargement of the heart, the apex being at the fifth intercostal space, 10 cm. from the midline. There were a blowing systolic murmur, transmitted to the axilla, and a snapping second sound in the aortic area. The liver appeared uniformly enlarged and firm in consistency, extending 8 cm. below the costal margin at the prolongation of the midclavicular line. Its borders were clearly palpable, there was no tenderness, and the surface seemed smooth. There was palpable splenomegaly but no enlargement of the lymph nodes. Bilateral Dupuytren's contracture of the palm of the hand was observed. The remainder of the physical examination was essentially negative.

Laboratory data disclosed the following: Urine was normal, except for the presence of bile. There were 9,400 leukocytes, with 70 per cent polymorphonuclears, 25 lymphocytes, 1 monocyte, 1 eosinophil and 2 basophils; erythrocytes numbered 3.73 million per cu. mm.; there were 13.5 gm. per cent of hemoglobin; the sedimentation rate was 59 mm. per hour, corrected. The Kahn test was negative. The non-protein nitrogen was 30, the fasting blood glucose 83 mg. per cent. Urea clearance by the maximum formula was 46 c.c./min., or 70 per cent of normal. The liver tests indicated the following values: direct reacting bilirubin, 7.4 mg.; total bilirubin, 8.8 mg. per cent; total cholesterol, 850 mg. per cent; plasma proteins, 7.56 gm. per cent; prothrombin time, 97 per cent of normal; alkaline phosphatase, 121.1 units; cephalin cholesterol flocculation, plus 4; thymol turbidity, above 20 units. The 24-hour urobilinogen determinations indicated .2 mg. in the urine and 25.0 mg. in the stools. The hippuric acid elimination was .6 gm. Roentgenograms disclosed a normal chest, stomach, duodenum and colon.

With a tentative diagnosis of cholangiolitic biliary cirrhosis, a laparotomy was performed on May 9, 1950. The liver was grossly enlarged, greenish and without nodular cirrhosis; a biopsy was taken. The extrahepatic biliary tract was permeable, and neither the common duct nor the gall-bladder was dilated. The duodenum was opened, the ampulla of Vater explored, and the bile ducts were opened and probed, but no abnormality could be found. A postoperative cholangiogram disclosed excellent visualization of the biliary system without evidence of obstruction.

The small bile ducts in the triads were the site of a very marked subacute to chronic inflammation. Each was surrounded by a concentrically placed band of connective tissue fibers and a variable but often rather intense infiltration of mononuclear cells, mostly lymphocytes and macrophages. In a few areas the inflammatory process was more acute, with focal destruction of the bile duct epithelium and moderate numbers of polymorphonuclear leukocytes. The larger bile ducts were partially collapsed and almost free from inflammatory reaction. There was little if any general increase in triadal connective tissue, and no proliferation of bile ducts. Many of the

FIG. 3. *Case 5.* Section of surgical biopsy obtained almost eight months after onset of symptoms. This Mallory-azan preparation shows a localized proliferation of collagen and infiltration of inflammatory cells in and around the portal triads. No fibrosis is seen within the lobules.

intralobular bile canaliculi contained inspissated bile casts, and some were surrounded by small nests of mononuclear cells. The parenchymal cells were free from visible bile and showed no evidence of degenerative change. They were uniform and arranged in an orderly pattern. The Kupffer cells were prominent but did not appear to contain pigment. No vascular abnormalities were seen.

The patient had a stormy postoperative course, with increasing jaundice, nausea and vomiting. On the ninth postoperative day her non-protein nitrogen was 119 mg. and a pericardial friction rub was noted. CO_2 at this time was 11.6 mEq. and chlorides 101.0 mEq. After large amounts of fluid were administered, the CO_2 values dropped, reaching normal within five days. Blood urea nitrogen likewise fell from a high of 61.4 mg. to 18.5 mg. The patient improved slowly and was discharged on June 5, 1950. Since then she has remained at home, with little improvement. The jaundice has remained essentially unchanged.

Case 6 (figure 4). A 64 year old white Austrian-born male, without previous significant history, on January 1, 1949, began to have loose stools with four to five bowel movements daily. There were associated fatigue and malaise. On the third day of this illness he noted that the stools had become somewhat clay-colored, that his urine was dark, and that jaundice had appeared in the sclerae and skin. The stools returned to a normal consistency on the fifth day, but the jaundice progressively increased and was accompanied by marked, generalized pruritus. There was a loss of nearly 45 pounds in weight during the next three months and the jaundice remained quite marked. A local physician recommended a bland diet, supplemented by additional protein, but this did not significantly alter the course of the disease.

Physical examination on admission, May 1, 1949, revealed a chronically ill, undernourished elderly male. Blood pressure was 118/80 mm. of Hg; pulse, 60 per minute. The most significant findings were in the abdomen, where a large nontender liver was palpable 10 cm. below the costal margin in the right midclavicular line. The spleen was not palpable, and there was pitting edema of both ankles. Otherwise, the physical examination was essentially normal. Laboratory findings indicated normal urine, except for the presence of bile. Blood counts showed 6,550 leukocytes with 85 per cent polymorphonuclears, 12 per cent lymphocytes and 3 per cent monocytes; 3.22 million erythrocytes per cu. mm.; hemoglobin, 10.5 gm. per cent. Sedimentation rate, corrected, was 26 per hour. The Kahn reaction was negative. Stools were negative for blood and parasites. Non-protein nitrogen was 21 mg. per cent; urea clearance by the standard formula was normal. Serum amylase was normal. Liver tests showed a direct reacting bilirubin of 18.64 mg., total bilirubin of 22.64 mg. per cent; total cholesterol, 355 mg. per cent, with 103 mg. esters. The total proteins were 6.96 gm., with 3.6 gm. albumin and 3.36 gm. globulin. Prothrombin was 77 per cent of normal; alkaline phosphatase, 23 units; cephalin flocculation was normal; thymol turbidity, 5.5 units. Measurement of the 24-hour excretion of urobilinogen indicated .05 mg. in the urine and 8.28 mg. in the stools. Roentgenologic examination of the chest, gastrointestinal tract and colon was essentially normal.

At laparotomy, performed on May 10, a greenish, uniformly enlarged, smooth liver was found without evidence of nodularity or metastasis. The gall-bladder did not appear distended, but rather collapsed, and the common duct and hepatic ducts showed no evidence of enlargement. The head and body of the pancreas were entirely normal. Stomach and duodenum appeared normal. The spleen was enlarged from three to five times its normal size, without perisplenitis. The liver was biopsied.

The liver sections disclosed a spectacular primary biliary cirrhosis (figures 4A and B). The small triads and the bile canaliculi showed an intense inflammatory reaction, and there was very striking proliferation of bile ducts and young fibrous tissue into the surrounding lobules. Most of the inflammatory cells were polymorphonuclear leukocytes, neutrophils and eosinophils, and were located next to the newly pro-

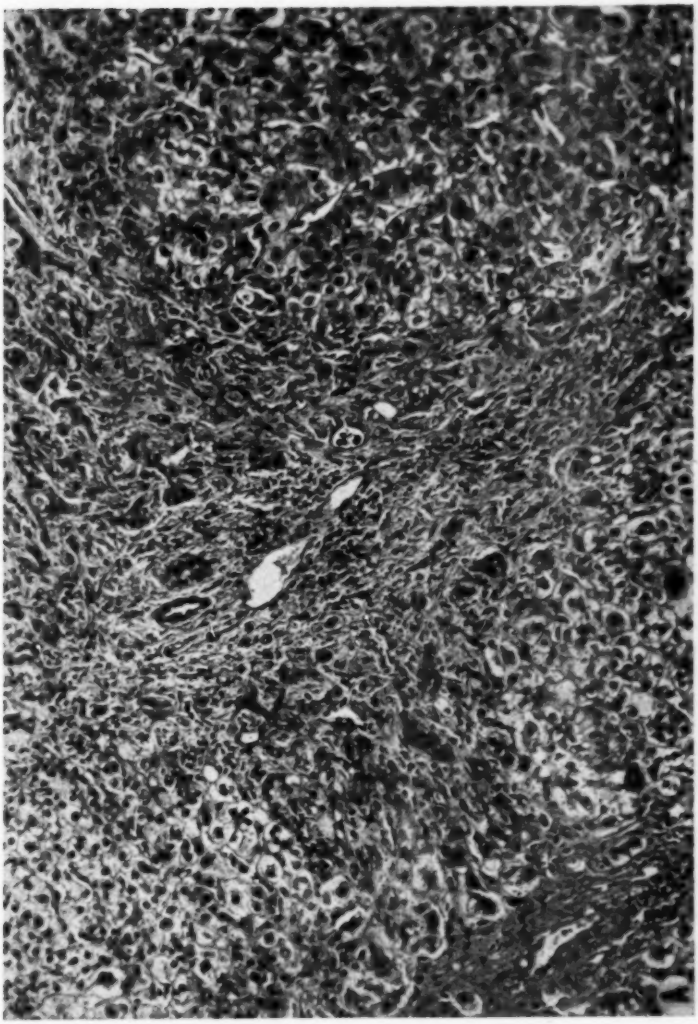

FIG. 4.4. *Case 6.* Section of a surgical biopsy removed about four months after the onset of jaundice and marked weight loss. The liver shows a very severe distortion of the triadal areas, with marked proliferation of bile ducts and loose collagenous tissue. Some intralobular extension of the inflammation is visible.

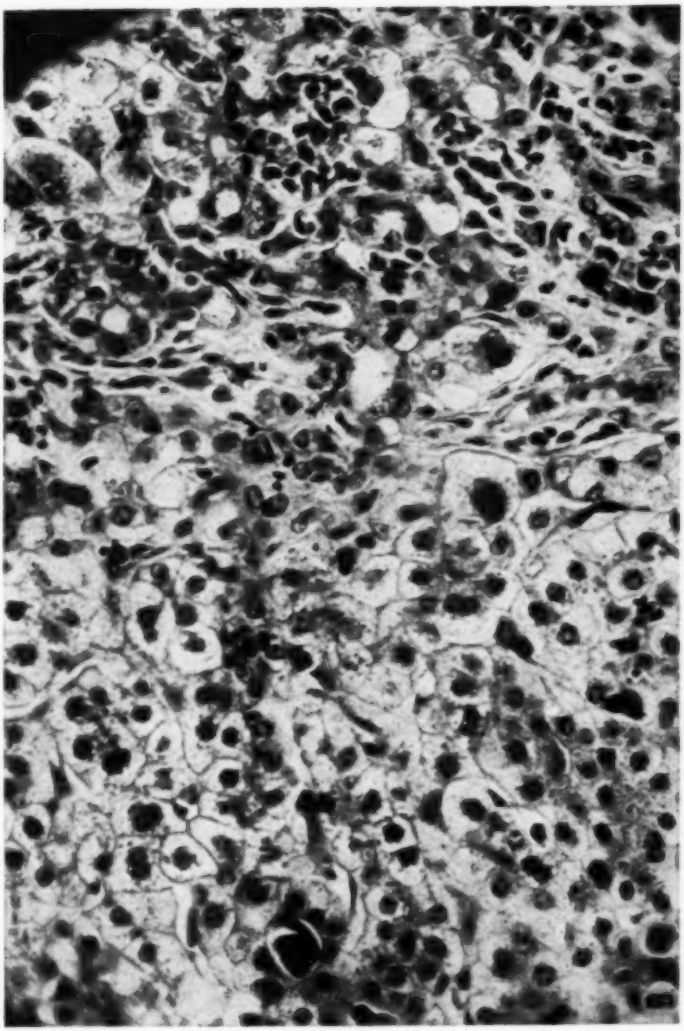

FIG. 4B. *Case 6.* Same section as figure 4A, under higher magnification, showing intense acute and subacute inflammatory exudate about the newly proliferated cholangioles. Note that only the hepatic cells near the inflamed areas show degenerative changes. Several bile pigment casts are seen.

liferated bile ducts and around the canaliculi. Inspissated bile was very marked in the canaliculi and the newly formed bile ducts. The larger triads were essentially normal, with little inflammatory cell infiltrate and normal undistended bile ducts and blood vessels. There were also marked accumulation of bile pigment in the hepatic cord cells and small amounts in some of the Kupffer cells. The lobular pattern was preserved, but the parenchymal cord pattern, particularly adjacent to the lobules, was distorted. Many of the parenchymal cells had a vacuolated cytoplasm, and there was marked variation in nuclear size. There were frequent binucleated and trinucleated cells, as well as cells with giant nuclei. No hyaline degeneration of parenchymal cells was seen. No vascular changes were seen.

The postoperative course was rather stormy, but the patient recovered. Tests repeated on the eleventh postoperative day disclosed findings similar to the previous ones. The patient was discharged on May 24, his condition and the jaundice essentially unchanged. His illness persisted and his course was progressively downward. He died at home five months after discharge. No autopsy was performed.

Case 7 (figure 5A). A 22 year old housewife without significant familial or past history noticed for the first time in February, 1938, the gradual onset of jaundice and pruritus in the skin, dark urine and light-colored stools. This was not accompanied by abdominal pain, chills, fever or infection of any sort. The patient did not discontinue her work. At no time did she have chills or fever. The menstrual periods became irregular in August of the same year. In the following 18 months she continued without much variation in the degree of jaundice. Upon admission, on October 10, 1939, she appeared to be a well developed, well nourished, moderately jaundiced adult female in no apparent acute illness. The blood pressure, pulse and respiration were normal. The spleen was enlarged to two inches below the costal margin, and the liver also appeared uniformly enlarged, nontender and firm, approximately 7 cm. below the costal margin in the midclavicular line, with a clear-cut anterior border. The rest of the physical examination was essentially negative. The urine was positive for bile but otherwise was essentially normal. There were 7,300 leukocytes (50 polymorphonuclears, 30 lymphocytes, 10 eosinophils and 2 basophils), 3.4 million erythrocytes per cu. mm., and 10.8 gm. of hemoglobin per 100 c.c. The total bilirubin was 3.7 mg. per cent; the plasma proteins were 8.7 gm. per cent, with 3.64 gm. albumin and 5.06 gm. globulin. The prothrombin time and galactose tolerance test were normal.

On November 16 the patient had a laparotomy. The liver was found to be enlarged and coarsely cirrhotic. Exploration of the gall-bladder, duodenum, pancreas and abdominal structures failed to reveal any changes other than in the spleen, which was enlarged to approximately four times its normal size and was adherent to the diaphragm and parietal peritoneum, with numerous moderately dense adhesions. A splenectomy was performed and a liver biopsy was obtained.

The histologic findings were as follows: The liver parenchyma was subdivided into multiple unilobular nodules by thin strands of connective tissue connecting adjacent triads. The connective tissue strands and the triads were rather densely infiltrated by mononuclear cells which often seemed centered about small bile ducts. There had been slight proliferation of the bile ducts of the smaller triads, and in places the connective tissue and the bile ducts seemed to infiltrate the lobule for short distances. In general, however, the lobular architecture and the liver cell pattern were preserved. The parenchymal cells were uniform and showed no degenerative change, except an occasional one with deep eosinophilic cytoplasm. A few bile canaliculi contained inspissated bile.

The patient recovered uneventfully from this operation. She was followed in the out-patient clinic at irregular intervals. She continued to be jaundiced, with slight variation in the degree of jaundice and with pruritus in the skin. Her men-

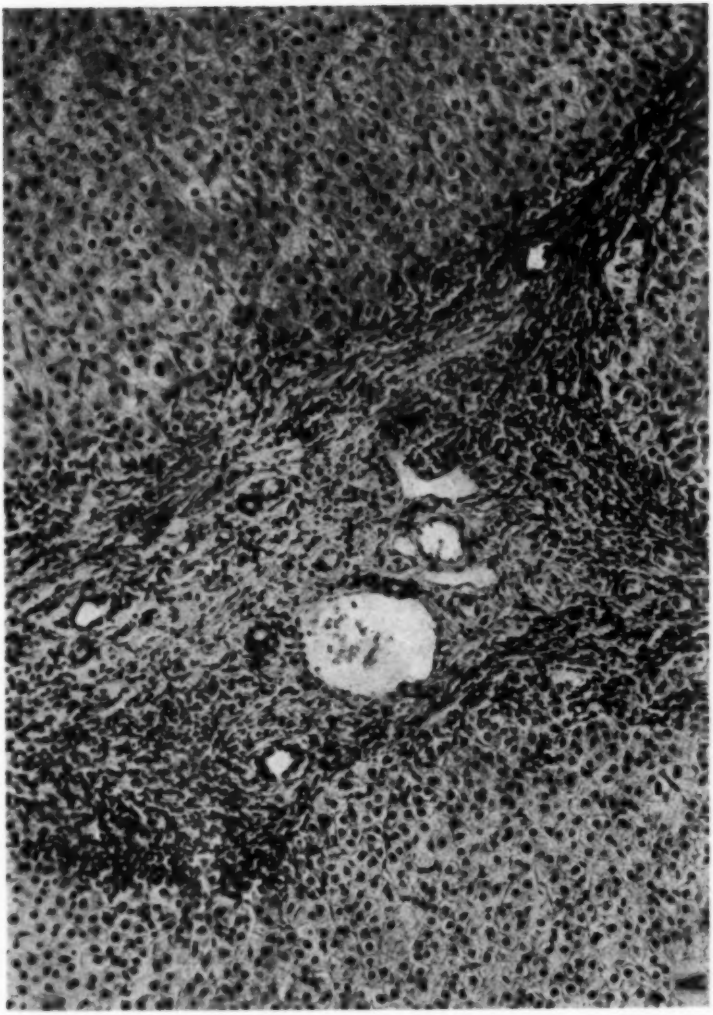

FIG. 5A. *Case 7.* Surgical biopsy of the liver, removed 18 months after onset of chronic jaundice. The photomicrograph illustrates the localization of the inflammatory reaction, particularly at the periphery of the enlarged triad and about the small bile ducts with well preserved parenchyma.

strual periods became more and more irregular and frequently she bled profusely. In April, 1943, she noticed some edema of the ankles and also distention of the abdomen with fluid. She was again hospitalized on May 17, 1943. As before, she appeared jaundiced and slightly undernourished. The liver, as before, was markedly enlarged, firm and hard. There were ascites and edema of the lower extremities. Bile was present in the urine, and the blood counts indicated 13,150 leukocytes (34 polymorphonuclears, 64 lymphocytes, 2 monocytes and 0 eosinophils), 11.5 gm. of hemoglobin and 3.16 million erythrocytes per cu. mm. The direct reacting bilirubin was 6.9 mg. and the total bilirubin 11.2 mg. per cent; the prothrombin time was normal; the total plasma proteins were 7.21 gm., with 2.29 gm. albumin and 4.91 gm. globulin; the total cholesterol was 160 mg. and the esters were 53 mg.

The patient was treated with diuretics and two paracenteses were done, and she was discharged, slightly improved, on June 17, 1943. She remained, as before, markedly jaundiced, and has not been seen since.

Case 8. A 41 year old housewife, without significant past or familial history, on August 14, 1930, at the age of 38, began to notice itching of her entire body. Soon afterward she noticed jaundice, light-colored stools and dark urine. These symptoms continued unchanged during the following months, the pruritus at times being unbearable. At the time of her admission to the hospital she had lost nearly 80 pounds. Physical examination on admission revealed an undernourished, markedly jaundiced, chronically ill woman. Hepatomegaly and slight splenomegaly were present, but otherwise physical examination was essentially normal. Laboratory data showed normal urine, except for the presence of bile. The blood counts were normal. Cholecystogram on September 17 disclosed normal visualization of the gall-bladder, without stones. Glucose tolerance test was essentially normal.

At laparotomy, on September 20, the gall-bladder was found to contain bile but no stones, and there was no dilatation of the extrahepatic biliary tract. The pancreas was soft. Several large lymph nodes were found along the common duct. The liver was found to be enlarged and greenish in color, and with a smooth surface. No liver biopsy was secured.

The postoperative recovery was uneventful, but the previous clinical state continued. Subsequently she was seen many times in the out-patient department at irregular intervals. Throughout this period the jaundice continued, appearing at times to be increased. In addition, the patient had had five to six loose stools daily since 1932, but these had not been bloody at any time. Hepatosplenomegaly persisted and the liver gave the impression of having further increased in size. The patient was re-admitted and on January 23, 1933, underwent a second laparotomy. This disclosed, as before, a large greenish liver, firmer in consistency and with a smooth surface. There was no obstruction or dilatation of the extrahepatic biliary tract. The spleen was considerably enlarged, to approximately five times its normal size. Cholecystoduodenostomy was performed. The postoperative course was stormy; the patient slowly failed and died on February 2, 1933.

At necropsy the abdomen disclosed a considerable quantity of bloody exudate. The liver appeared much enlarged and firm, its capsule irregularly thickened by adhesions. Seen through the capsule, the parenchyma revealed accentuation of the lobules, presenting the appearance of a fine, even, slightly nodular surface. Section of the parenchyma against increased resistance revealed a firm, slightly protuberant, shiny green surface. All lobular markings were accentuated, appearing as pale green elevated areas surrounded by translucent stroma, and ranging up to 2.0 mm. in diameter. The liver weighed 3,150 gm. All of the periportal lymph nodes were enlarged, edematous and a mottled dark gray in color. The bladder was thin-walled and contained several small, multifaceted pigment stones. There was no scarring of the liver tissue about the gall-bladder. In the loose fat at the lateral wall of the gall-

bladder was a fresh hematoma measuring 6 cm. in diameter. The common duct was slightly dilated, with a circumference of 1.3 cm. It was patent and its mucosa faintly bile-stained. The larger hepatic ducts were also patent. The spleen weighed 700 gm. and had a firm shiny capsule, slightly roughened by adhesions. Section disclosed a fairly dark red pulp containing small irregular gray Malpighian bodies.

Microscopically, the splenic capsule was thinned, and the sinuses contained a large quantity of blood, fibrin, leukocytes and serum. The stroma was scant. Serum and fibrin were so abundant that the splenic pulp presented a picture less cellular than normal. There were many small infarcts.

The periportal lymph nodes disclosed slightly thickened capsules, with evident increase of the stroma due to the new connective tissue formation. The lymph sinuses were all dilated, many containing macrophages and bile pigment; polymorphonuclear leukocytes, lymphocytes and mononuclear cells were also present.

The liver sections showed a marked fibrosis, with frequent connection of adjacent portal triads by rather vascular young connective tissue. In addition, there were strands of connective tissue infiltrating the lobules from the portal triads. There were many lymphocytes and a few plasma cells in the connective tissue. The large bile ducts were not remarkable, and the smaller junctional ducts were conspicuous by their absence. There was slight to moderate proliferation of new bile ducts. There was marked bile stasis in the canaliculi and hepatic cells near the portal triads. The lobular and cell cord pattern was well preserved, and the liver cells were uniform and showed no evidence of degeneration.

The anatomic diagnosis was as follows: biliary cirrhosis (Hanot type). Marked icterus. Recent postoperative cholecystoduodenostomy. Icteric nephrosis. Multiple small traumatic hematomata; hematoma of the right suprarenal gland. Bilateral simple ovarian cysts with recent hemorrhage of the ovaries. Hyperplasia of the spleen. Acute dilatation of the right heart. Chronic mitral endocarditis (rheumatic), with mild stenosis. Patchy chronic fibrous pericarditis. Localized adhesive peritonitis, recent and chronic. Hyperemia and edema of the lower lobes of both lungs. Fibrous obliterative pleuritis (left). Small infarct in the spleen.

Case 9 (figure 5B). A 16 year old male without significant past or familial disease developed diarrhea in the spring of 1936 averaging six stools daily; this condition persisted in the following years. Previous to that time he had never been ill. In the autumn of the same year he developed jaundice and a feeling of distention in the right upper quadrant of the abdomen. A physician diagnosed enlargement of the liver and a laparotomy was subsequently performed, but no lesion was found in the extrahepatic biliary tract or gall-bladder. One month later, in view of the persistent jaundice, the same surgeon operated once more but again was unable to locate any obstruction of the extrahepatic biliary tract. Recovery was uneventful but marked jaundice with associated pruritus persisted. There was a cumulative loss of approximately 15 pounds of weight.

On admission to this hospital, August 8, 1938, examination revealed a well developed, undernourished adult male in no great distress. Blood pressure was 130/50 mm. of Hg; pulse, 94; respirations, 20 per minute. The liver extended 2 to 3 cm. below the costal margin in the midclavicular line, and the spleen was palpable 8 to 9 cm. below the costal margin. Physical examination was otherwise not remarkable. Proctoscopy disclosed a friable, easily bleeding, diffusely granular rectal mucosa, presenting the typical appearance of chronic nonspecific ulcerative colitis. Except for the presence of bile, the urine was normal. Blood counts disclosed 4,400 leukocytes, with 58 polymorphonuclears, 34 lymphocytes, 4 monocytes, 2 eosinophils and 2 basophils; 4.1 million erythrocytes per cu. mm., and 11.5 gm. per cent of hemoglobin.

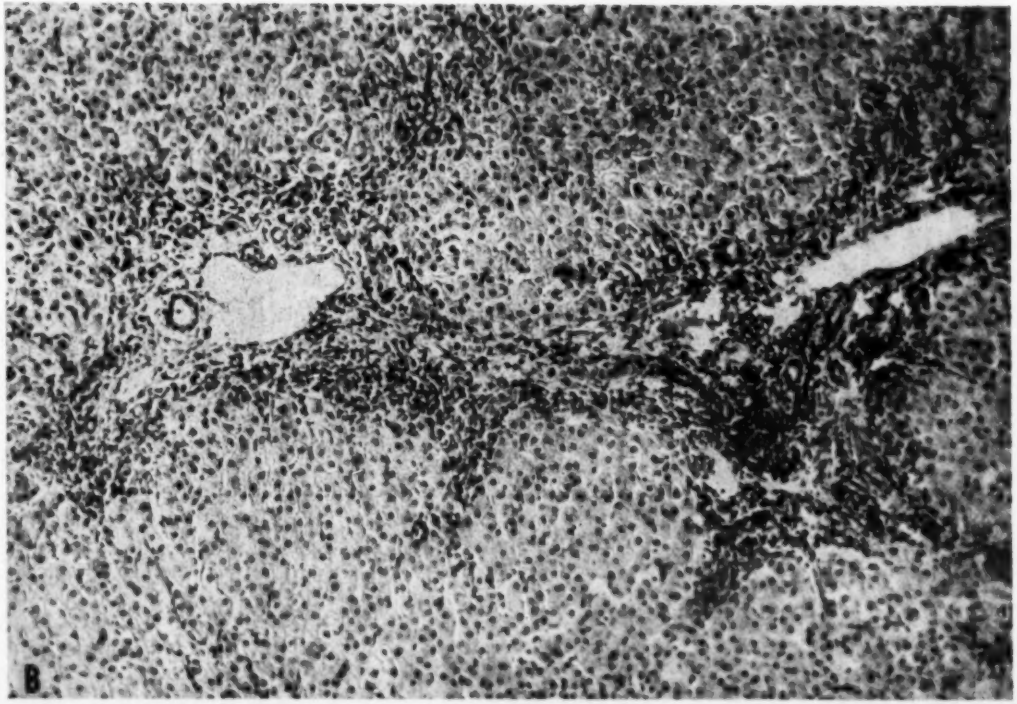

FIG. 5*B*. *Case 9.* Surgical biopsy of the liver, obtained about two years after the onset of continuing jaundice and enlarged liver. Note the intense inflammatory reaction in the triads, especially surrounding the smaller bile ducts. The finger-like extension of the inflammatory reaction into the lobules is well shown.

On September 8 a second laparotomy was performed. As with the previous explorations, no obstruction or dilatation of the extrahepatic biliary tract or gallbladder was found. The liver appeared enlarged and greenish yellow, with a smooth surface. The transverse colon was markedly contracted and the serosa definitely hyperemic. The spleen appeared to be enlarged to about five times its normal size and was dark red in color, with several flecks of fibrinous exudate on its surface. A liver biopsy was done.

The sections showed the liver parenchyma to be subdivided into large and small spherical areas with no relationship to liver architecture. Some of the liver islands had triads in the center, some at the edges, and in some no vascular or bile duct elements were seen. The connective tissue septa which caused this disorganization of the parenchymal structure varied from thin cords to extremely broad bands of rather mature connective tissue element a lobule in width. The large bile ducts seen in these bands as well as in the triads showed no evidence of acute or chronic inflammation either in or surrounding them, although there was a rather dense diffuse inflammatory process in the triadal connective tissue consisting mostly of lymphocytes and a few polymorphonuclear leukocytes. Occasional small finger-like fibrous projections extended out from a few of the portal triads and contained newly formed small bile ducts and a denser infiltration of inflammatory cells with a higher proportion of polymorphonuclear leukocytes. Both these areas and small areas of inflammatory cells within the parenchyma suggested an intralobular pericholangitis and cholangiolitis. There was only a small quantity of visible bile pigment in either liver canaliculi or hepatic cells. The cell cords were badly disorganized, and many of the nodules of liver tissue had the definite appearance of having been recently regenerated. These and the marked variation in size of the liver cells, as well as the presence of binucleated forms, suggested recent active cell proliferation. There was little evidence of active degenerative changes.

Postoperative recovery was slow and the symptoms remained unchanged. The patient has not been seen since 1938.

Clinical Picture

On the basis of clinical features, cholangiolitic biliary cirrhosis may be subdivided into two different forms:

A. *Xanthomatous Biliary Cirrhosis:* In the last century and early in the present one, Addison and Gull [13] and others [14, 15] described this condition precisely. The observations made here in two cases are in agreement with prior observations.[8, 16, 17] Ages vary from 27 to 35, which is within the range observed earlier.[16-18] The two cases were females, this disease being exceptional in males. In none of the cases studied was there a familial incidence, an observation substantiated by MacMahon and Thannhauser.[17]

Among the characteristic clinical features it was observed that the onset of jaundice and the disease was insidious. Jaundice and pruritus were prominent prior to the appearance of xanthomatosis in the skin. Pruritus was marked in both cases, and in one case the administration of bile salts by mouth, prescribed elsewhere, was immediately followed by a considerable aggravation of the itching. Hepatomegaly was present in both cases, the liver being grossly and uniformly enlarged, firm and nontender. Splenomegaly likewise was observed in both cases. The course of the jaundice was chronic, although of varying intensity. No evidence of peripheral

lymphadenopathy was observed. Xanthomatosis was present in one (case 1), whereas in the other (case 2), only xanthelasma had developed after one and one-half years of the disease. In both cases, darkening of the skin was observed without increased pigmentation of the mucosae. Biopsies of the skin in both cases disclosed only increased melanin pigment. Edema, ascites and increased abdominal collateral circulation were conspicuously absent, as observed previously.[17] Several authors have indicated the persistent hyperlipemia occurring in these cases,[19] and Ahrens and Kunkel [20] have recently found that xanthomatosis is always associated with persistent hyperlipemia above 2,000 mg. per cent. Resolution of the xanthomatosis occurs following a drop in the serum lipemia, clearly illustrating the mutual relationship.[20, 21] No significant loss of weight, malnutrition or fever was observed. None of the cases had any history of chills, fever or pain in the right upper quadrant. While darkening of the urine and progressively light-colored stools were observed, the stools were never described as pale yellow or clay-colored.

B. *Non-xanthomatous Cholangiolitic Biliary Cirrhosis:* This condition has been accurately described since the last century.[22-24] The entity is known by various designations: biliary cirrhosis of Hanot, cholangitis lenta,[7, 8] intrahepatic cholangitic biliary cirrhosis,[6] interstitial chronic hepatitis with liver hypertrophy,[22] nonobstructive cholangitic biliary cirrhosis,[5] chronic intrahepatic obliterating cholangitis,[4] cholangiolitic biliary cirrhosis,[2] and others. In these cases it was observed that the age in the seven cases studied ranged widely from 10 to 64, and that the disease occurred in both sexes (four in females and three in males).

There were associated diseases in four of these cases. In two, it occurred in the course of a chronic nonspecific, ulcerative colitis (cases 4 and 9); a third had rheumatoid arthritis (case 3), and a fourth had hypertensive cardiovascular disease. There was no apparent associated disease in the remaining three cases.

The onset of jaundice was rather rapid, but the course was chronic. Fever, pruritus and weight loss were present in all cases. In one (case 6), the patient lost 45 pounds in a period of three months. The onset of jaundice was accompanied by urine containing bile salts. The stools were described as considerably lighter, but no complete obstruction was apparent in any case.

Hepatomegaly was observed in six of the seven cases at the first examination; the seventh, who showed no apparent hepatomegaly at the onset of jaundice, in the course of two years developed a firm, hard, uniformly enlarged, nontender liver. Splenomegaly was observed in five of the seven cases, and in another (case 6), it was disclosed at laparotomy. Pruritus was prominent in five cases and present sporadically in the other two.

The degree of jaundice varied considerably during the course of the disease. In five cases it was quite marked and in the other two, mild, below 10 mg. per cent of total bilirubin. Collateral circulation of the abdomen

was not present in any case. Edema of the extremities occurred in one undernourished male (case 6) who had lost 45 pounds in three months, and in another (case 7) ascites followed profuse menstrual bleeding. Although pain in the right upper quadrant was detected in two cases, there was no biliary colic, chills or fever. Dark urine containing bile was present in all cases, and light-colored stools in three.

Liver Tests

In view of the fact that biochemical determinations, with the exception of abnormal lipemia, were similar in cases with and without xanthomatosis, these tests will be considered together. The findings mentioned above agree in the main with recent studies in 10 cases by Dauphinee and Sinclair.[25]

Bilirubin: There was increased bilirubinemia (direct reacting and total) in all of the seven cases studied. The degree of bilirubinemia varied considerably; in most cases, total bilirubin was below 10 mg. per cent, but in one it reached a level of 22.6 mg. per cent.

Alkaline Phosphatase: In every case the values were markedly elevated, the lowest being 23 and the highest 131 (in a case without xanthomatosis).

Cholesterol and Cholesterol Ester Values: Elevation of cholesterol was found in every case, without an associated increase in cholesterol esters, so that the cholesterol-cholesterol ester ratio was lowered. High levels of cholesterol occurred in two cases without xanthomatosis. The lipids measured in cases with and without xanthomatosis were within the range observed by Ahrens and Kunkel.[20] Total sera lipid values exceeded 1,800 mg. in all cases with xanthomatosis.

Prothrombin Time: Subsequent to the intravenous administration of vitamin K, no hypoprothrombinemia was observed in any case.

Hippuric Acid: In one of the four cases tested, excretion of hippuric acid was less than 0.7 gm. The test in this case, with an excretion of 0.6 gm., was invalidated because of the presence of hypertensive cardiovascular disease with inadequate kidney function and decreased urea elimination.

Urinary Urobilinogen: No instance of increased urinary urobilinogen values occurred among the five cases tested.

Fecal Urobilinogen: Three cases out of five revealed values below 10 mg.; none, however, reached a level of 5 mg., indicating that obstruction of the biliary tract was not complete.

Plasma Proteins: The total plasma proteins were not uniform in this group. In three of the seven cases, albumin values were slightly decreased, with globulin elevation in every case.

Cephalin-Cholesterol Flocculation and Thymol Turbidity: Thymol values were abnormal in every case, five of the seven being highly positive. The cephalin-cholesterol flocculation was abnormal in all cases but one.

Electrophoretic Separation of Serum Proteins: Elevation of the beta globulins was disclosed in every case that was measured, forming a pattern

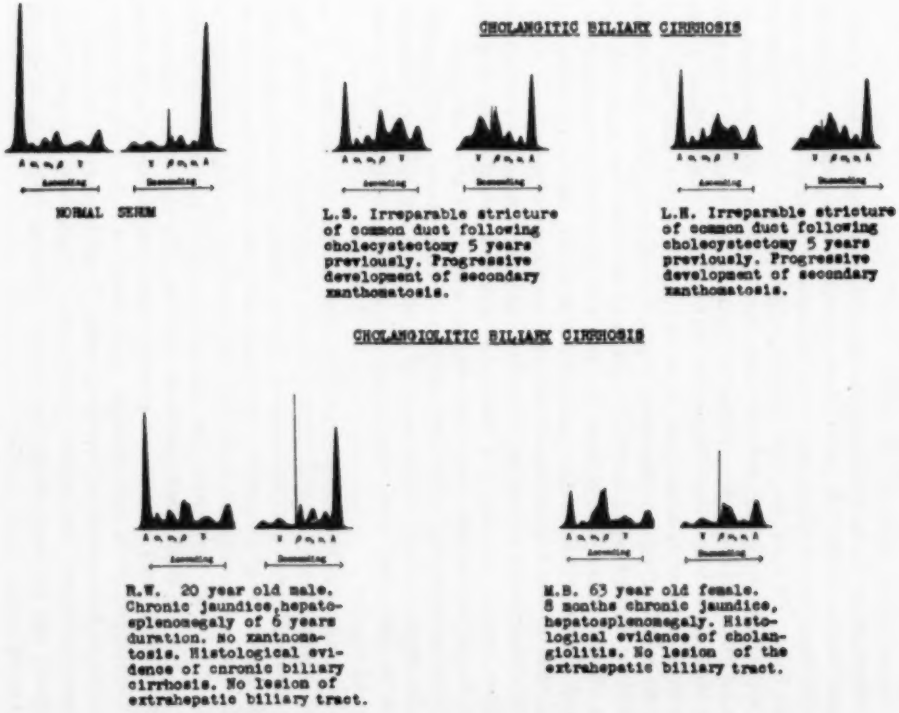

FIG. 6. Electrophoretic patterns of serum proteins in biliary cirrhosis.

similar to that described by Gray and Barron [26] and Kunkel and Ahrens.[27] A similar pattern is also revealed in cholangitic biliary cirrhosis.[28] These values are illustrated in figure 6 and table 1.

Pathologic Findings

Observations on the gross morphology of the liver were made in seven of the nine cases. In five, the observations were made at laparotomy within one year of the onset of symptoms. The outstanding feature was enlargement of the liver. Of these, four had an enlarged greenish liver (cases 6, 5, 1 and 8) with a smooth surface; the fifth (case 4) also had an enlarged greenish-looking liver, which was described as having an uneven surface. In another, also observed at laparotomy 18 months after the onset of symptoms, a firm, enlarged, greenish-looking liver with a smooth surface was found. A slightly nodular liver was described in case 8 three years after the first observation; and in another (case 1), eight years after the first laparotomy and nine after the onset of symptoms, the liver was described as moderately enlarged, granular and fibrotic, and interpreted grossly as "portal cirrhosis." A hobnail nodular appearance was not observed in any of the cases.

Histologic observations were made in eight of the nine cases. In seven of these, surgical biopsies were obtained at laparotomy, and in two by punch liver biopsy; in another, tissue observations were made after necropsy.

The histologic study of the liver sections revealed no features distinguishing the cases having xanthomatosis from those which did not; therefore, all of the eight cases from whom tissue was available for study will be summarized together.

The most significant lesion was found in the smaller bile ducts of the small lobular triads (junction ducts or canals of Hering) and in the finer bile canaliculi. In all of the sections studied, there was an apparent pericholangiolitis. In four of the eight cases there was also evidence of acute destruction of the epithelium of the small bile duct radicles, with acute inflammatory cells permeating the lumina of these ducts. In the material from six of the eight cases, there was a definite decrease in the number of visible mature small bile ducts, suggesting a destructive process as described by Klemperer.[4] In six of the eight cases there was also evidence of proliferation of new immature bile ducts, either at the borders of the triads or projecting out into the lobular parenchyma. These newly formed ducts, elongated and tortuous, were usually lined by rather large pale cells, with little or no luminal space visible.

There was an increase of fibrous connective tissue in all cases studied, but its extension and quantity varied considerably from one case to another. It was marked enough to connect adjacent triads in four cases. Marked intralobular fibrosis was observed in five cases, with finger-like connective tissue prolongations extending well into the lobule.

Destruction of the lobular architecture and the cord pattern was seen in only two (cases 1 and 9), although in one of these (case 1) a histologic observation made eight years previously indicated preserved lobular pattern. If the process is of sufficient chronicity, extensive fibrosis, fragmentation and disappearance and regeneration of the lobules without active inflammatory features apparently may be found. Then the histologic diagnosis may be difficult, and it might be interpreted as portal cirrhosis,[17] as it was in the second biopsy from case 1 of this series. Here the situation is not unlike that seen in chronic renal disease, where the terminal stage is often difficult to classify with only morphologic criteria.

Another distinguishing feature was the almost constant preservation of the parenchyma, with no evidence of fatty or hyaline degeneration or distortion of the cord pattern. Minor to marked changes in the parenchyma were limited to the periphery of the lobule immediately adjacent to the pericholangiolitis and to the areas of proliferation of the bile canaliculi and fibrosis. In these areas there were sometimes large hepatic cells with granulated cytoplasm, multiple nuclei and degenerative features.

When intralobular infiltration of inflammatory cells occurred, it was usually centered around the non-epithelized bile canaliculi. In two cases, minute accumulations of inflammatory cells within the lobule could not be localized with certainty about the canaliculi.

The presence of bile in casts within the lobule was apparent in all cases with marked jaundice but did not appear prominent in the two cases with minimal increase of bilirubinemia (cases 1 and 4). Bile was also frequently seen in the Kupffer cells and in the hepatic cells. The larger bile ducts did not appear distended, nor did they contain bile casts.

This study shows that the main histologic features of this form of intrahepatic biliary disease seem to be a more or less chronic inflammation in and around the smaller bile ducts and bile canaliculi, accompanied by frequent perilobular and intralobular bile duct proliferation and, in most cases, by a decrease in the number of the smaller bile ducts. In a few instances, actual necrotizing cholangitis of the smaller bile radicles was present. Unless the disease is very chronic, it can usually be distinguished from portal cirrhosis by the preservation of the lobular architecture and liver cord pattern and the absence of significant diffuse cellular degeneration or regeneration. The morphologic features differed markedly from active viral hepatitis. The diffuse necrobiotic changes seen in infectious hepatitis were not found in cholangiolitic biliary cirrhosis, and marked proliferation of the small bile ducts has not been observed in viral hepatitis.

Primary biliary cirrhosis or primary intrahepatic cholangiolitis and pericholangiolitis is usually grossly differentiated from secondary biliary cirrhosis by the absence of obstruction of the large bile ducts and of stasis of bile in them present in the latter disease.[29, 30] Microscopically, the presence of an inflammatory reaction about the smaller bile ducts without inflammation

of the larger bile ducts may be useful histologic criteria in differentiating primary intrahepatic biliary disease from obstructing and ascending cholangitis. On the other hand, a histopathologic survey [31] of a number of cases of the obstructive cholangitic type has revealed that, in several instances, significant inflammation of the larger ducts was absent at the time the observation was made, although the smaller bile ducts and canaliculi were chronically affected. Again, an analogy with renal disease may be appropriate. It is often very difficult to distinguish hematogenous pyelonephritis from ascending pyelonephritis on morphologic grounds, although the etiology and pathogenesis of the two diseases are very different. A similar comparison might be made between obstructive cholangitis and primary cholangiolitic hepatic disease.

Extravasation of bile or "bile granulomas" was rare; it occurred in only one case (case 6) in one area. Miliary or large septic abscesses are not uncommon in septic obstructive ascending cholangitis but were not found in primary biliary cirrhosis.

Etiology and Pathogenesis

The pathogenesis of cholangiolitic biliary cirrhosis is still controversial. Thannhauser and Magendantz [32] had suggested that there were evidences of obstruction of the bile ducts produced by the xanthoma cells in cases of biliary xanthomatosis. Histologic observations made by Rössle [2] and MacMahon [17] demonstrated that the process is centered around the smaller bile ducts and biliary canaliculi and that there are no xanthoma cells present. The present study confirms these observations, and furthermore discloses that lesions similar to those described by MacMahon [17] in xanthomatous biliary cirrhosis are present in the forms without xanthomatosis, known in the literature as Hanot's biliary cirrhosis. It is not apparent in the cases with xanthomatosis why the level of serum lipids is very high and continues elevated for considerable periods of time. It is possible that obscure hormonal factors may play an important rôle, as indicated in one case (case 1), in which the hyperlipemia and hyperbilirubinemia decreased considerably while the patient was pregnant. Furthermore, it has been emphasized by others [16, 17] that xanthomatosis occurs almost exclusively in adult females. This was true in the cases observed by us. However, it is also certain that intrahepatic biliary cirrhosis may occur in adult females without accompanying xanthomatosis. In obstructive cholangitic biliary cirrhosis, the hyperbilirubinemia and hyperlipemia are secondary to the obstructive features producing bile regurgitation. They rapidly subside when the obstruction is released.

The fibrosis in the cases reported in this study appeared in the areas where the pericholangiolitis was present, and varied in degree and extension with the severity of the inflammatory features. In cases in which clinical regression of the disease had occurred, the active inflammatory features

around the bile canaliculi had also almost entirely disappeared, leaving only areas with fibrosis (cases 1 and 4).

At present there is no clear concept regarding the factors responsible for the chronicity of the biliary canalicular inflammation. It is quite possible, however, that many cases with cholangiolar involvement do not follow a chronic course.

The type of jaundice in cases with cholangiolitic biliary cirrhosis has many characteristics similar to those observed in obstructive lesions of the extrahepatic biliary tract. In both, there are many similar pathologicophysiologic features with regurgitation of bile into the blood.[22] In cholangiolitic biliary cirrhosis there are manifestations of obstruction at the level of the finer biliary radicles producing intralobular regurgitation of bile, as indicated by the presence of intralobular casts or plugs and absence of dilatation or stasis of the larger biliary ducts. This intrahepatic regurgitation of bile is apparently conditioned by the activity of the inflammatory process in the biliary radicles and canaliculi and not by the degree of fibrosis. This is indicated by the fact that in cases where there are subsidence and disappearance of symptoms and findings with clearance of the hyperlipemia, jaundice and pruritus, the fibrosis persists. The clinical features of the disease are present in cases with subacute initial cholangiolitic changes even though the fibrosis has not as yet developed or is minimal in degree.

The etiologic factors responsible for the cholangiolitis are a matter of controversy and are as yet hypothetic. La Manna [7, 8] and others [34–37] have interpreted the process as a descending cholangitis, a hematogenous infection that involves the smaller bile canaliculi. This hypothesis is very appealing but has not been proved conclusively. As has been pointed out above, primary cholangiolitic biliary cirrhosis would then be related to obstructive biliary cirrhosis in much the same manner as hematogenous pyelonephritis is related to ascending pyelonephritis. Recent studies [38] have indicated that cholangitis and cholangiolitis may occur in streptococcus and staphylococcus infections. In the past it has been difficult to obtain adequate material from which to isolate organisms possibly responsible for the process. Postmortem cultures are practically useless because of the agonal invasion of organisms from the intestine. With the aid of modern punch biopsy for specimens, valuable material should be secured for much needed bacteriologic studies. As will be pointed out in the discussion of treatment of this disease, recent encouraging experience with chemotherapy offers one of the strongest evidences of the infectious nature of this disease.

Hanger and Gutman [39] and others [40] have interpreted these cases as toxic, postarsphenamine hepatitis. Experimental observations [41] have also shown that manganese salts may produce changes in the bile ducts with proliferation of the bile canaliculi, which somewhat resembles those observed in primary biliary cirrhosis. In none of the present series of cases was there a history of previous jaundice, previous toxic hepatitis or exposure to toxic substances.

Eppinger [42] and lately others [1] have interpreted primary biliary cirrhosis as secondary to viral hepatitis, although no viral agent for this condition has ever been demonstrated. In our experience, fibrosis following viral hepatitis can be separated histologically, functionally and clinically from cholangiolitic biliary cirrhosis. Viral hepatitis is primarily a hepatocellular disease, with necrobiosis of the parenchyma. Infiltration of the parenchyma and portal triads by inflammatory cells, mostly mononuclear, does occur. Accumulations of these cells in the triads do not, however, convey the impression of cholangiolitis and pericholangiolitis. In primary biliary cirrhosis there is preservation, to a great extent, of the parenchyma of the liver and cord cells, a feature emphasized by Hayem [22] in 1874, and in modern studies.[17] When there is involvement of the lobule itself, it appears to be because there is a concentric invasion from the periphery of the lobules from the areas of pericholangiolitis. Massive necrosis in viral hepatitis, which is unusual, probably leads to subacute yellow atrophy and small contracted livers in a certain small percentage of cases. Cholangiolitis consistently leads to hypertrophy and enlargement of the liver. The results of functional and electrophoretic studies in cholangiolitic biliary cirrhosis resemble those in obstructive disease of the biliary tract and not parenchymatous liver disease.

Treatment

As the etiology of primary biliary cirrhosis is not known at present, the treatment of this condition is largely empiric. In cases with hyperlipemia and xanthomatosis, a vegetarian diet, low in cholesterol, has been advised.[19] A low fat diet was given to one of the patients of this series (case 1), without significant change in the degree of lipemia, jaundice or xanthomatosis. Administration of choline, inositol and lipocaic was also found to be ineffective. Ahrens and Kunkel [20] described different agents used in 18 cases of xanthomatous biliary cirrhosis, without any significant alterations in the serum lipids. Among these were a cholesterol free diet, a low fat diet, a high protein diet, thyroid, soybean lecithin, serum albumin intravenously, alpha-tocopherol, nitrogen mustard, intravenous or intramuscular injections of liver extract and lipocaic. They found that desoxycholic acid appeared to produce a decrease in serum lipids in two cases. A full diet, including fat supplemented with fat soluble vitamins, was considered necessary for adequate nutrition.

The chronic course of the disease may be interrupted by a spontaneous drop in the lipemia and hyperbilirubinemia, with disappearance of xanthomas as described by Riisfeldt-Pederson [21] and Ahrens and Kunkel.[20] Of particular interest are the recent French reports [43-46] describing subsidence of symptoms and abnormal findings with decrease of the total lipids, cholesterol and thymol turbidity test, and disappearance of xanthomatosis following intensive penicillin treatment with doses of from 1 to 3 million units daily. Cattan et al.[46] have described a case treated with such therapy in whom

lipemia and hyperbilirubinemia disappeared and electrophoretically the abnormal peak of beta globulins disappeared. A therapeutic approach leading to the eradication of the inflammation of the smaller bile duct canaliculi, using chemotherapy and antibiotic therapy, seems to be reasonable and worthy of further trial.

Discussion

Cholangiolitic biliary cirrhosis is an inflammatory process centered in and around the smaller bile ducts and canaliculi or cholangioles.[1] Clinically, there are two forms to consider: with and without xanthomatosis. The histologic features do not help in differentiating one from the other. The metabolic disorder leading to xanthomatosis, suspected of being in part a primary disorder because it occurs almost exclusively in adult women, is probably related to the primary obstructive biliary disease with bile regurgitation. Biliary xanthomatosis has been observed in the past [18-47] and also by us [21] in several cases of cholangitic infectious obstructive disease of the biliary tract. There is also persistent hyperlipemia in these cases. The relation between forms of cholangiolitic biliary cirrhosis, with and without xanthomatosis, is of particular interest since the recent studies of Ahrens and Kunkel,[20] which have demonstrated that only cases with prolonged elevation of the total serum lipids developed xanthomatosis. These authors, by determining the total lipid level at frequent intervals, were able to predict which patients would develop generalized xanthomatosis in the skin. The changes in the serum lipids in disease of the biliary tract are subject to variation depending on the degree of bile regurgitation, due to obstruction, infection and the patient's nutrition. It has been previously indicated that, while obstructing features tend to raise cholesterol, acute biliary tract infection, malnutrition and parenchymatous liver disease tend to lower its values.[48]

A primary biliary cirrhosis without xanthomatosis as described by Hanot [24] is considered an extremely rare form of cirrhosis by many authors, and its existence is even questioned. This is apparently due to the fact that many of these cases are not properly diagnosed and rarely come to pathologic observation. There is only one in the present series of cases who came to necropsy.

The chronic jaundice and other chronic features of the disease are due, most probably, to the type of pathologic involvement, rather than to the action of a single pathogenetic agent. Fibrosis is apparently due to the sclerosing action of the inflammation and bile regurgitation. The fibrosis (cirrhosis), then, to a certain extent, cannot be interpreted as primary, since it is secondary to the cholangiolitis, the initial process. In the present study, only cases with cholangiolitis with a chronic course leading to fibrosis have been included but it is quite possible that many cases do not have a chronic course. This was evident in one case (observed, but not reported here) who had a laparotomy for an apparent obstruction of the extrahepatic biliary

tract. No lesion of the extrahepatic ducts or gall-bladder was found at operation. A liver biopsy indicated cholangiolitis and pericholangiolitis. The patient's course was favorable, and clinically there was a complete remission of symptoms. Unfortunately, no serial studies were made. Similar cases have also been observed by other authors.[49]

It is significant that the histologic structure of the liver parenchyma revealed remarkable preservation, except in the immediate areas near the smaller bile ducts and canaliculi, a finding noted since the last century,[22] as well as in modern studies.[17] This agrees with studies of parenchymal function tests, such as urinary urobilinogen, hippuric acid and prothrombin time determinations, which were not significantly altered, thus contrasting markedly with those noted in parenchymatous liver diseases, such as viral hepatitis. It seems difficult to harmonize these observations with the opinion of Eppinger [42] and others,[1] that cholangiolitic biliary cirrhosis is either a form of parenchymatous liver disease or is secondary to parenchymatous liver disease.

Summary

Ten cases of long-standing cholangiolitis and pericholangiolitis are described. There was no involvement, obstruction or dilatation of the extrahepatic biliary tract, the lesion occurring around the smaller bile ducts, with secondary fibrosis in these areas (so-called primary biliary cirrhosis).

Cholangiolitic biliary cirrhosis has two clinical forms:

A. With xanthomatosis: xanthomatous biliary cirrhosis. Two female patients without familial incidence of the disease were observed. Chronic jaundice, hepatomegaly, splenomegaly, xanthomatosis and pruritus were the most conspicuous clinical features. Edema, ascites and collateral abdominal circulation were absent. There was no significant loss of weight, malnutrition, history of chills, fever, or pain in the right upper quadrant.

B. Without xanthomatosis: non-xanthomatous biliary cirrhosis (Hanot's biliary cirrhosis). Seven cases were observed, three males and four females, ranging in age from 10 to 64 years. There was no familial incidence of the disease. Fever, jaundice, loss of weight and pruritus were present in all. Hepatomegaly was observed initially in six cases; in the seventh, in which onset of the disease occurred while the patient was under observation in the hospital, the liver later became hard and firm. Clinical splenomegaly was present in five cases, and in another, enlargement of the spleen was found at laparotomy. The degree of jaundice varied considerably but followed a chronic course in all cases. Increased collateral circulation of the abdomen was not found in any case. Edema of the extremities appeared in one undernourished male who had suffered a loss of 45 pounds in weight in a period of three months, and ascites was observed in a female following a marked loss of blood during menstrual periods.

Biochemical determinations indicated similar deviations in both types of cases. Evidence of bile regurgitation was present, such as elevation of the

direct reacting bilirubin, total cholesterol and alkaline phosphatase, the last showing a quite considerable elevation, from 23 to 121 Bodansky units, and minimal or no alteration in the tests expressing hepatic function. The urinary urobilinogen, hippuric acid and prothrombin values when measured were not significantly altered. Tests based upon the altered colloid stability of the sera, such as thymol and cephalin cholesterol flocculation, were abnormal in all cases but were rather unpredictable in the degree of fluctuation. This is probably due to the complex alterations in proteins and lipids of the sera. The persistent, very high hyperlipemia observed in cases with xanthomatosis (serum lipids above 2,000 mg. per 100 c.c.) was not observed in the nonxanthomatous cases.

Electrophoretic separation of the serum proteins in both types of cases disclosed the distinctive peak elevation of the beta globulin fraction characteristic of biliary cirrhosis.

Grossly the liver was seen to be enlarged, with a smooth or slightly nodular surface but without the hobnail appearance. Histologic studies disclosed inflammatory features in and around the smaller intrahepatic bile ducts, junction ducts or in the canaliculi between the lobules. The inflammatory features were essentially perilobular but sometimes extended into the lobule, distorting the adjacent cells. The small biliary ducts often proliferated and became tortuous and elongated. The large biliary ducts were unobstructed and collapsed. The degree of scarring was variable. In general, the liver parenchyma was strikingly preserved and without fatty, degenerative or diffuse necrobiotic features. Changes in the parenchyma were present only in the neighborhood of the bile ducts.

While the above observations supply no additional information as to the pathogenic organisms responsible for the pericholangiolitis, it seems probable from the clinical, functional, electrophoretic and pathologic findings that this process is primarily an inflammation in and around the smaller bile canaliculi. Fibrosis seems to be secondary to these alterations (primary biliary cirrhosis). There is no evidence that it is a parenchymatous liver disease or a condition secondary to parenchymatous liver disease.

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EVALUATION OF THE LIVER BIOPSY *

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DIRECT inspection of the liver is desirable in suspected hepatic disease.[1, 2, 3, 4] The purpose of this paper is to present a comparison of gross impression and histologic diagnosis. A series of normal and diseased livers was examined peritoneoscopically. Biopsies were obtained under direct vision, using needle and forceps technics. We also wish to present our opinion as to the comparative adequacy of needle and forceps biopsies.

There are many detailed clinical studies of hepatic disease based on liver function tests and biopsy.[5, 6] Disagreement exists regarding correlation of liver function tests with structure. This disagreement is generally acknowledged. Most histopathologic studies are based on the blind punch technic. We feel that the true pathologic state of the liver cannot always be determined in this manner, and that the tiny bits of tissue obtained by the needle method are often inadequate for diagnosis. Accurate diagnosis is best afforded by a complete clinical, laboratory and microscopic evaluation, to which a fourth—endoscopic examination—has been added.

MATERIALS AND METHODS

This paper is based on 135 consecutive patients whose livers were examined by peritoneoscopy and biopsies obtained. Of these, 45 had cirrhosis, 25 were normal, 22 had fatty metamorphosis, 18 had hepatitis, 13 had metastatic carcinoma, three had malignant lymphoma, three had extrahepatic obstruction, two had cholangiolitic cirrhosis, two had hepatomegaly of unknown causes, and one each had polyserositis and sarcoidosis.

Biopsies were obtained in each case after careful inspection of the liver. In 53 cases biopsies were obtained by the Vim-Silverman needle punch technic, and in 76 cases with the peritoneoscopic biopsy forceps. In six cases both technics were used. Single biopsies of the right lobe were obtained in 61 instances, and of the left lobe in 32 instances. Both lobes were biopsied in 20 cases, and multiple biopsies were taken from the same lobe in 22 cases.

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Needle biopsies were obtained from the anterior surface of the liver by introducing the needle through the abdominal wall, or through an intercostal space, and by guiding the needle to a selected site under direct vision. Those obtained with the forceps were obtained from the edge of either or both lobes at a site selected to represent best the structural state of the entire organ.

Results

In 100 (74 per cent), the gross and microscopic diagnoses were the same; in 19 (14 per cent), the gross and microscopic diagnoses were at variance; and in 16 (12 per cent), the biopsies (all of which were obtained by the needle technic) were considered inadequate for microscopic diagnosis.

Ten of the 19 cases in which the gross and microscopic diagnoses were at variance were considered at the time of direct examination to be diffuse hepatic fibrosis and fatty metamorphosis, but microscopically seven were normal and two showed only mild cholangitis. In four of the 19 cases, metastatic carcinoma of the liver was considered to be obvious but the biopsy specimens did not include neoplastic tissue. One patient with carcinoma of the pancreas appeared to have a normal liver, but a small metastasis was seen in the microscopic section. One liver which appeared cirrhotic showed normal histology. One case of subacute bacterial endocarditis, in which the liver appeared to be greatly enlarged, was considered to be normal microscopically. A case called normal, and another called hepatomegaly of unknown cause, proved to be severe fatty metamorphosis. One case was called early fatty metamorphosis grossly and showed only focal cellulitis.

Discussion

These results indicate a close correlation between the gross and microscopic appearance of the liver. Gross diagnoses are based on the size, surface configuration, color and texture (indicated by the "feel" of the biopsy forceps on cutting through liver parenchyma). The peritoneoscopist and pathologist nearly always agreed on normal and seriously diseased livers. The most apparent difference of opinion occurred in early stages of disease, particularly fatty metamorphosis or beginning diffuse fibrosis. Fifty per cent of the disparity in the gross and microscopic diagnoses involved these conditions. Usually the microscopist was unable to confirm the gross impression of early disease.

Biopsies obtained with the forceps technic were much superior to needle biopsies. In the latter, the sections often contained such small portions of lobules that they were frequently inadequate for an accurate histologic diagnosis. In some instances the tissue was considerably traumatized by the needle, further reducing the value of a biopsy already of questionable worth because of its minute size.

However, some of the sections obtained with the Vim-Silverman punch technic were adequate for diagnosis. In these cases the lesions were usually rather diffuse.

It was relatively easy to decide whether a given biopsy was normal or abnormal microscopically. In those cases in which the biopsy was felt to represent an abnormality, the following changes were readily interpreted:

1. Fatty metamorphosis. (Figure 1*a*)
2. Bile stasis—the degree of bile stasis is consistent with the degree of jaundice noted clinically. It is possible to determine rather accurately from the specimen the degree of jaundice. (Figure 1*b*)
3. The changes of cirrhosis. (Figure 1*c*)
4. Metastatic neoplasm and malignant lymphoma. (Figure 1*d*)
5. Nonspecific granuloma. (Figure 1*e*)
6. Cholangitis.

The following changes, although recognizable as abnormalities from minute specimens of tissue, are less easily interpreted:

1. Toxic hepatocellular changes. (Figure 1*f*)
2. The presence of scattered inflammatory cells in the liver sinusoids. (Figure 1*g*)
3. Fibrotic changes near the liver capsule. (Figure 1*h*)
4. Small foci of necrosis.

The biopsy should be large enough to include an entire lobule or sufficient parts of lobules to permit evaluation on a lobular basis. Few needle biopsies satisfy this requirement (figure 2*a*). The great majority of biopsies obtained through the peritoneoscope contain considerably more tissue than is necessary to satisfy this requisite (figure 2*b*). We feel that on certain of the smaller biopsies it is impossible to make a specific diagnosis as to type and degree of liver damage.

Infectious hepatitis is a diagnosis which is often difficult for the pathologist to make from single or even multiple liver biopsies. In the mild cases a pathognomonic picture is not seen and the liver may not be involved uniformly in all areas. It is usually necessary to correlate the histologic picture with function tests, clinical history and other evidence to reach a final clinical diagnosis of infectious hepatitis.

Another type of hepatopathy difficult to diagnose on single specimens is the mild hepatocellular damage of nonspecific type seen in senile livers, and in association with severe systemic disease.

To reiterate: For final diagnosis a correlated clinical and pathological study is necessary. Both direct examination of the liver through the peritoneoscope and more adequate biopsies obtained under direct vision aid greatly in arriving at a correct final diagnosis.

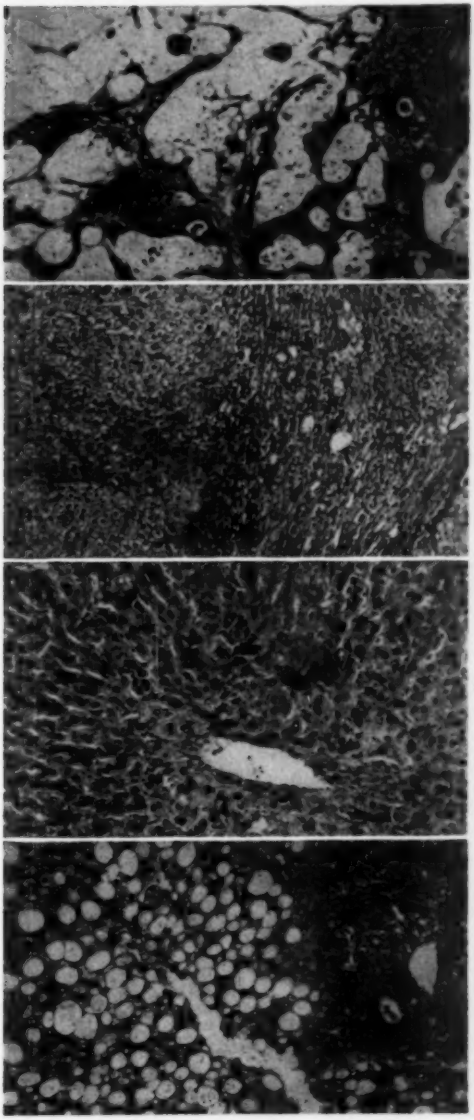

FIG. 1a. Fatty metamorphosis. H&E stain × 100. *b*. Plugs of inspissated bile in canaliculi from case of obstructive jaundice. H&E stain × 100. *c*. Portal cirrhosis. H&E stain × 100. *d*. Adenocarcinoma metastatic to liver. H&E stain × 100.

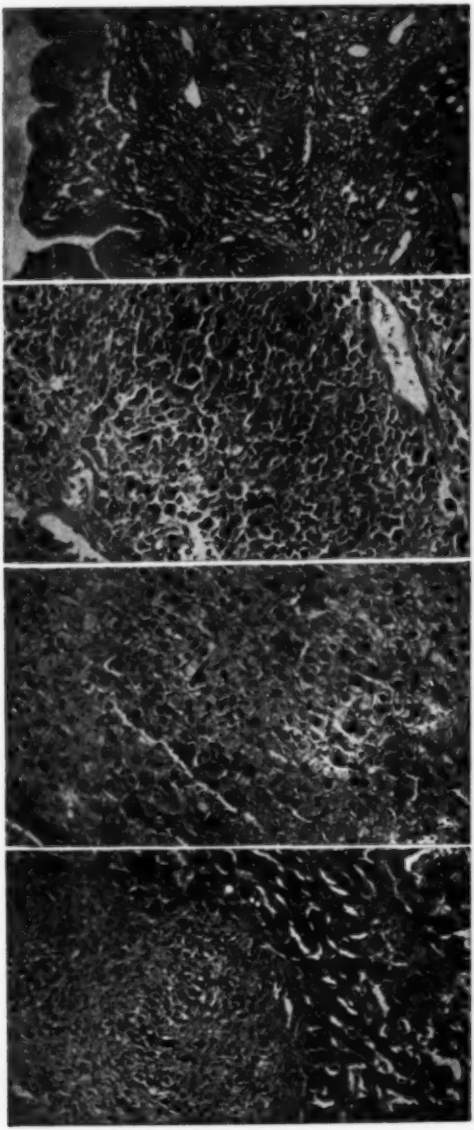

FIG. 1e. Nonspecific granuloma. H&E stain × 100. *f*. Toxic hepatocellular changes. H&E stain × 100. *g*. Scattered inflammatory cells in liver sinusoids. H&E stain × 200. *h*. Subcapsular fibrosis. H&E stain × 100.

a *b*

FIG. 2*a*. Biopsy obtained with Vim-Silverman needle. H&E stain × 10. *b*. Biopsy obtained with peritoneoscopic forceps. H&E stain × 10.

SUMMARY AND CONCLUSIONS

1. There is a close correlation between the gross and the microscopic picture of hepatic disease (74 per cent of this series).

2. Biopsy of the liver by the forceps method is more satisfactory for routine purposes than the Silverman punch technic.

3. The changes readily elicited by biopsy of the liver are: fatty metamorphosis, bile stasis, cirrhosis, metastatic neoplasm and malignant lymphoma, nonspecific granuloma and cholangitis.

4. Recognizable but less easily interpreted are: toxic hepatocellular damage, scattered inflammatory cells in liver sinusoids, fibrotic changes near the liver capsule, and foci of necrosis.

The considerable difference of opinion existing in the literature about whether the histologic picture correlates with liver function tests may be

explained by the fact that needle biopsies are often inadequate for histologic diagnosis.

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AN ANALYSIS OF THE PHENOMENON OF "ANTICIPATION" IN DIABETES MELLITUS*

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IN the second edition of Darwin's *The Variation of Animals and Plants Under Domestication*,[1] published in 1894, it is stated that the rule with respect to the age of onset of a hereditary disease in parent and child is inheritance at a corresponding period of life. It was noted, however, that "when the rule fails the disease is apt to come on earlier in the child than in the parent; the exceptions in the other direction being very much rarer." Nevertheless, investigators were finding frequent exceptions to the rule for many different diseases with a variable age of onset; and in 1901, Pieraccini,[2, 3] impressed by these "exceptions," defined the "law of anticipation" in mental disorders as the onset of a hereditary disease at a progressively earlier age in successive generations of an affected family.

Anticipation, or antedating, as it is sometimes called, has been extensively discussed in mental diseases with a familial incidence, where it has been claimed that anticipation is the result of a progressive deterioration of the germ plasm. This view was clearly expressed by Mott,[4] who stated, "The general tendency is for insanity not to proceed beyond three generations. . . . As a rule there is a regression to the normal or the stock dies out. Not infrequently the stock dies out by the inborn tendency to insanity manifesting itself in the form of congenital imbecility or insanity of adolescence. . . ."

The view mentioned in the preceding paragraph has become accepted not only with respect to mental disorders but also with respect to many other illnesses with a familial incidence. In the case of diabetes, this deduction rests mainly on the work of Woodyatt and Spetz.[5] They concluded from their analysis of the histories of 100 consecutive families in which the disease occurred in at least two generations that, on the average, the age of onset of diabetes advances approximately 20 years per generation and that this advance holds even if diabetes is not manifested in one generation. Hence, if a grandparent of a child is diabetic, the age of onset of diabetes in the child will tend to be 40 years less than the age of onset in the grandparent, even though neither of the child's parents is diabetic. Woodyatt and Spetz emphasized the practical applications of their findings in relation to the estimation of the probability that the disease will appear in as yet

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unaffected relatives of diabetic patients. In summary, these conclusions are that the onset of diabetes will usually occur 20 years earlier and rarely, if ever, later than the onset in the parent or in relatives of the parents' generation; if diabetes develops in one child in a family, the disease will develop at about the same age in his sibs and cousins who may become diabetic—in older sibs at a later age than in younger sibs. Woodyatt and Spetz agreed with Mott that anticipation results from a progressive degeneration of the germ plasm.

Most geneticists do not ascribe any biologic significance to the phenomenon of anticipation. They consider it to be a statistical rather than a biologic phenomenon. This opinion is based on general considerations rather than actual investigation, since little work has been done to substantiate it and the work that has been done has been largely speculative. Thus, Penrose,[6] in his analysis of anticipation in pedigrees of dystrophia myotonica, stated that "the tendency for anticipation to occur in pedigrees of hereditary disease is due to the manner of their selection and is not a phenomenon of direct biological significance." However, Penrose did develop a possible genetic (that is, biologic) mechanism, based on a hypothesis advanced by Goldschmidt,[7] which could lead to the observed data. We know of no analysis in which anticipation was actually demonstrated to be a statistical phenomenon.

Because of the practical implications in medicine and the theoretic implications in genetics, anticipation has been much considered by workers in both fields, and many investigators have felt that more data and particularly more intensive analysis of the data with regard to possible statistical defects in the method of collection or analysis are desirable. These possible sources of error, which were noted more than 35 years ago by Pearson [8] and Heron,[9] have been discussed in detail by Paterson [10] and reviewed recently by Penrose.[6] They are of many types and are difficult to avoid unless considerable care is exercised. It follows, therefore, that even though data may appear most convincing, considerable caution must be shown before they can be accepted as proving that antedating is of physiologic importance in any given disease.

Consequently when, in the course of collecting family histories for a study of the genetics of diabetes, 251 histories in which one parent of the patient was also diabetic became available, it was decided to review them in the hope of adding information that might help to clarify the situation. A preliminary report of this review based on fewer cases and a more limited analysis has been published in the *Proceedings of the Staff Meetings of the Mayo Clinic*.[11] The results of the genetic study will appear elsewhere.

The Data

Family histories were taken from consecutive patients who had the diagnosis of diabetes entered on their Mayo Clinic record for the first time

during the current visit. Among a total of 1,379 patients in this series, 251 reported one parent diabetic and 15 reported both parents diabetic. Information with regard to the patient's parents, siblings, spouse and children was obtained by interviewing the patient. No attempt was made to confirm the data obtained from the patient except in the rare instances in which a relative named in the history also was a patient of the clinic. Although special pains were taken in all instances to secure accurate information, the data, nevertheless, are subject to the errors introduced by the vagaries of recalling ages and illnesses of close relatives.

In the collection of family histories of diabetic patients, the most likely sources of error are as follows: (1) until the introduction of insulin in 1922, many persons with early onset of diabetes did not live to become parents; (2) despite the introduction of insulin, diabetic women, until very recently, produced relatively few viable offspring; (3) family histories collected at clinics where diabetes or its symptoms are the reason for the patient's attendance tend to be those of patients with relatively severe diabetes and therefore the histories of patients with earlier ages of onset than the average.

Each of these factors tends to force the data into a pattern showing anticipation when in fact none may exist. The first two sources of error are inherent in the data collected at the clinic, just as they are in histories collected elsewhere, and as a consequence few, if any, diabetic parents are found with onset of diabetes prior to age 30 years (one out of 200 in the present sample). The third source of error is of little importance in the data to be presented, because only approximately 40 per cent of the 1,379 patients from whom these special histories were obtained came to the clinic because of previous knowledge of diabetes or because of the presence of symptoms of diabetes. The remaining 60 per cent came to the clinic for reasons not associated with diabetes, although about 80 per cent of them knew they had diabetes. At any rate, the biases that may exist in the data are of such a nature as to enhance any tendencies toward anticipation that may be there.

The present sample confirms Woodyatt and Spetz's [6] observations that the age of onset is lower in the child than in the parent in the majority of the family histories, and that in those cases in which the age of onset is lower in the child, the average advance in age approximates two decades. However, if anticipation is involved as a physiologic phenomenon, the age of onset of diabetes in children of groups of diabetic parents with the same age of onset should average less than that of the parents regardless of the age of onset in the parents; for example, using two decades as the age difference, the average decade of age of onset in children, one of whose parents became diabetic in the fifth decade (ages 40 to 49 years) should be the third (ages 20 to 29 years). The data are presented in table 1. A comparison of the average age of onset in the patients (last line of table 1) with the age of onset in the parents demonstrates that the average age of onset in the off-

TABLE I

Relation Between the Age of Onset in a Parent and the Age of Onset in the Patient

Age of Onset in the Patient, Years	Age of Onset in the Parent, Years							Total	Age of Onset in the Parent Unknown
	20–29	30–39	40–49	50–59	60–69	70–79	80–89		
0–9			1					1	
10–19	1	1			2			4	
20–29			4	2	1			7	3
30–39		2	12	8	5	1	1	29	8
40–49		1	15	20	26	8	3	73	16
50–59		2	3	19	18	9	4	55	13
60–69			2	9	7	6	2	26	9
70–79				2	2	1		5	2
Total	1	6	37	60	61	25	10	200	51
Average age of onset in the patients, years	16	40	41	50	49	54	52	48	50

spring is neither 20 years nor any other constant number of years less than that of the parent, and that the average age of onset in the child is not lower than that of the parent until the age of onset in the parent falls in the age interval 60 to 69 years.

Nevertheless, clinical experience indicates that in a majority of the cases in which a parent and a child are diabetic the age of onset in the child is lower than in the parent. As has already been indicated, the data of the present study are no exception. A summary of the figures in table 1 shows that in 67.5 per cent of the cases the onset of diabetes was in an earlier decade in the patient than in the diabetic parent. An explanation is required.

It will be shown in the following that the observed frequency of prior onset in the child is what is to be expected when the age of onset in the child is physiologically independent of that in the parent. Column 2 of table 2, based on the data of Joslin and associates [12] comprising 12,740 cases, shows the frequency with which the onset of diabetes occurs during or before an indicated decade of life. It is reasonable to assume that these data, which were collected over a long period at an excellent and famous diabetic clinic, are representative of the situation among diabetic patients in general and may be applied to the present data. On the basis of these figures, it may be concluded that 31.6 per cent of all diabetics would have become diabetic before the age of 40 years; 54.1 per cent would have become diabetic prior to 50 years of age; 81.1 per cent before 60 years, and so forth. It should be emphasized that in the foregoing, the age of onset in any given individual is in no way influenced by the age of onset in the other individuals in the population. If it is assumed that the age of onset in the parent *in no way influences the age of onset in the child* (that is, that anticipation is not a physiologic phenomenon), it is possible, by making use of the data of table

1 and column 2 of table 2, to compute the frequency with which a diabetic child would be expected to become diabetic in an earlier decade of life than its diabetic parent. The calculations are as follows: Column 3 of table 2 shows the percentage frequency with which the onset of diabetes occurred in the indicated decades among the 200 diabetic parents of this sample for whom the age of onset was reported; thus, 3.0 per cent of the parents became diabetic during the age interval 30 to 39 years, 18.5 per cent during the ages of 40 to 49 years, and so forth. Since it has been assumed that the age of onset of diabetes in the child is not influenced by the age of onset in the parent, it follows that 19.4 per cent of the children of the 3.0 per cent of the parents with age of onset in the age interval 30 to 39 years will be expected to become diabetic before reaching the age of 30 years; hence, $0.194 \times 0.030 \times 100 = 0.6$ per cent of all the children with diabetic parents will be born of parents whose diabetes began in the age interval 30 to 39 years and will themselves have become diabetic prior to this age; similarly, $0.316 \times 0.185 \times 100 = 5.8$ per cent will have been born of diabetic parents with age of onset in the period 40 to 49 years, and will themselves have become diabetic at an earlier age, and so on through the last age interval, 80 to 89 years. The calculations predict that, on the average, 64.3 per cent of all family histories collected from families in which diabetes occurred in two successive generations and in which the age of onset in the parents is distributed as in this sample would be expected to show "anticipation." In the present sample, 67.5 per cent of the pertinent family histories showed such anticipation.

As was pointed out in the preliminary report of this material,[11] it is difficult to compute the expectation for Woodyatt and Spetz's data because they published only the difference in age of onset between the parent and

TABLE II

The Frequency with Which, in This Sample, a Diabetic Child Would Be Expected to Have an Earlier Age of Onset Than the Diabetic Parent

1	2	3	4
Age, Years	Percentage Frequency of Onset in or Prior to the Indicated Decade*	Percentage Frequency of Onset in the Indicated Decade Among the Parents	Expected Percentage Frequency of Onset in an Earlier Decade in the Children
0–9	4.9		
10–19	11.8		
20–29	19.4	0.5	0.1
30–39	31.6	3.0	0.6
40–49	54.1	18.5	5.8
50–59	81.1	30.0	16.2
60–69	96.4	30.5	24.7
70–79	98.8	12.5	12.0
80–89	100.0	5.0	4.9
Total		100.0	64.3

* Based on data of 12,740 cases published by Joslin and associates.[12]

the child and not the actual ages of onset; also, because there seem to be internal contradictions in their paper concerning numbers of cases. It appears, however, that the onset of diabetes in the child anteceded that of the parent by 10 or more years in 65 per cent of their cases. This value, which is almost identical with the value which would be expected (64.3 per cent) if the distribution of the age of onset in the parents of Woodyatt and Spetz's sample is the same as in the present sample, is not strictly comparable to that computed for the present sample because it is based on a difference in age of onset of at least 10 years, rather than the age of onset occurring in a different decade. A comparable value would be somewhat greater.

Harris [13] has recently published the data of 1,241 family histories collected from diabetic patients. In 109 of these families one of the patient's parents was also diabetic. These data may be used to test further the hypothesis advanced in previous paragraphs. They are listed in table 3. Here

TABLE III

Relation Between Age of Onset in a Parent and Age of Onset in the Patient
(Based on Data from the Appendix of Harris's[13] Paper)
(Only Cases in Which One Parent Was Diabetic Are Included)

Age of Onset in the Patient, Years	Age of Onset in the Parent, Years							Total	Age of Onset in the Parent Unknown
	20–29	30–39	40–49	50–59	60–69	70–79	80–89		
0–9		2						2	
10–19	1	4	7	1				13	
20–29		1	4	3	4			12	2
30–39		4	7	6	9	1		27	4
40–49		1	4	4	7	1		17	5
50–59			3	3	2	6	1	15	10
60–69									2
Total	1	12	25	17	22	8	1	86	23
Average age of onset in the patients, years	15	23	31	36	39	51	53	35	46

again, it is clear that the average age of onset in the offspring is not any constant number of years less than that of the parents. The marked apparent correlation between the age of onset in parent and child in these data is probably a consequence of the way the data were selected and not an indication of a true correlation. Harris stated that a large proportion of his cases were collected in a children's clinic. The parents of these children are still young, and hence those of them who will become diabetic later in life are not, for obvious reasons, included in the table. Harris, after analyzing these data, wrote as follows: "It seems reasonable to conclude . . . that the age of onset of the disease in the propositus is not correlated, or only slightly correlated, with the age at onset in the diabetic parents."

In Harris's sample the decade of the age of onset was earlier in the child than in the parent in 71 of the 86 (82.6 per cent) parent-child pairs. Because the distribution of the age of onset in this sample is very different from that of other samples (compare column 2 of tables 2 and 4), the computation of the expected frequency cannot be based on the data of Joslin and associates [12] but must be based on the age distribution found in this sample. The computations are carried out exactly as were those for table 2. The results, listed in table 4, show that the expected frequency of antedating is 73.1 per cent, which compares favorably with the 82.6 per cent observed.

The larger difference between the observed and expected ratios in this series, as compared to the two series discussed previously, probably is due to the fact that the 23 cases comprising those in which the age of onset in the affected parent was not known are not a random sample of the 109 cases

TABLE IV

The Frequency with Which in Harris's[10] Sample a Diabetic Child Would Be Expected to Have an Earlier Age of Onset Than the Diabetic Parent
(See Text for Further Explanation)

1	2	3	4
Age, Years	Percentage Frequency of Onset in or Prior to the Indicated Decade	Percentage Frequency of Onset in the Indicated Decade Among the Parents	Expected Percentage Frequency of Onset in an Earlier Decade in the Children
0–9	10.6	—	—
10–19	25.5	—	—
20–29	40.7	1.2	0.3
30–39	58.7	14.0	5.7
40–49	76.2	29.0	17.0
50–59	96.0	19.8	15.1
60–69	99.8	25.5	24.5
70–79	100.0	9.3	9.3
80–89	100.0	1.2	1.2
Total		100.0	73.1

with one parent affected. The average age of onset in this group of patients is 46 years, as contrasted to 35 years for the remainder of the group; the difference is significant ($X^2_{(1)} = 17.40$; $P < 0.001$). Furthermore, in nine of these 23 cases, antedating could not occur because the age at death of the affected parent was either in the same decade as, or in an earlier decade than, the age at which the patient became diabetic. Hence, the maximal frequency of prior onset in this group is 60.9 per cent, as contrasted with 82.6 per cent in the 86 cases in which the age of the parent at onset was known.

In those cases in which the onset is earlier in the child than in the parent, the average age difference is approximately 20 years (Woodyatt and Spetz [8] and the present sample). Calculations essentially similar to but more detailed than those explained previously indicate that in the present sample the average difference expected on the assumption of no relation between the age of onset in parent and child is 21 years, and the observed difference

19 years. The predicted value is probably too high, because it is based on computations which include cases in which the age of onset in the offspring antecedes that in the parent by 60 or more years, cases that are very likely to be missed in clinical data. If these cases are eliminated from the calculations, the expected difference in age of onset in those cases in which the onset is earlier in the child than in the parent becomes 19 years.

Among the reasons for the reluctance of some workers to consider the phenomenon of anticipation as being of physiologic significance are the facts that no instance of anticipation has been discovered in animals other than man and that no satisfactory biologic explanation for it has been offered. In the case of diabetes, however, there is a possible biologic rationale for anticipation when the patient's mother is diabetic. This may be based on the recognition that many infants born of prediabetic and diabetic women

TABLE V

Relation Between the Age of Onset in the Mother and the Age of Onset in the Patient

Age of Onset in Patient, Years	Age of Onset in the Mother, Years						Total	Age of Onset in Mother Unknown
	30–39	40–49	50–59	60–69	70–79	80–89		
0–9		1					1	
10–19	1			2			3	
20–29		3	2				5	1
30–39	1	8	3	4	1		17	3
40–49	1	10	14	17	3		45	6
50–59	1	2	11	13	7	3	37	8
60–69		2	2	4	4	1	13	6
70–79			1	1	1		3	1
Total	4	26	33	41	16	4	124	25
Average age of onset in the patients, years	37	40	48	48	55	57	47	53

evidence characteristic abnormalities [14] (reviewed by Barns and Morgans [15]). It may be assumed that this unfavorable uterine environment causes earlier onset of diabetes among the offspring in whom the disease will subsequently develop. This does not apply when the patient's father is the affected parent because children of diabetic fathers do not suffer from these disabilities.

On the basis of the published data it seems likely that the effect of the unfavorable uterine environment would be most marked in those cases in which the mother was diabetic at the time of the birth of the patient or became diabetic within 15 years after the birth of the patient. Almost all of these cases would be included among those in which the mother became diabetic prior to age 50 years. Comparison of the average age of onset of the patient when the age of onset of the mother occurred during the age

intervals 30 to 39 years or 40 to 49 years with that of the group whose fathers became diabetic during the same age intervals (last lines of tables 5 and 6) shows no age difference for the latter period and an eight-year spread for the former period. This difference is due to the patient with onset in the age interval 10 to 19 years (table 5). The average age of onset for all the cases in which the mother became diabetic prior to age 50 years is 40 years and is identical with the average age of onset of those patients whose fathers became diabetic prior to age 50 years.

The data may be examined further by comparing the frequency of antedating when the mother is the affected parent with the frequency when the father is the affected parent. The values, which are 70.9 per cent and 64.8 per cent, respectively, are not significantly different ($X^2_{(1)} = 1.053$; $P > 0.3$). Finally, it may be noted that the frequency of prior onset in

TABLE VI

Relation Between the Age of Onset in the Father and the Age of Onset in the Patient

Age of Onset in Patient, Years	Age of Onset in the Father, Years							Total	Age of Onset in Father Unknown
	20–29	30–39	40–49	50–59	60–69	70–79	80–89		
10–19	1							1	
20–29			1		1			2	2
30–39		1	4	5	1		1	12	5
40–49			5	6	9	5	3	28	10
50–59		1	1	8	5	2	1	18	5
60–69				7	3	2	1	13	3
70–79				1	1			2	1
Total	1	2	11	27	20	9	6	76	26
Average age of onset in the patients, years	16	45	41	52	51	52	49	49	47

those cases in which the affected parent became diabetic before age 50 years is 43.3 per cent when the mother is the affected parent and 42.9 per cent when the father is the diabetic parent. It seems reasonable to conclude, therefore, that the unfavorable uterine environment provided the fetus by diabetic or prediabetic mothers is not a major factor in determining the age of onset of diabetes in their diabetic offspring.

COMMENT

The analysis presented demonstrates that the data on which the evidence for anticipation rests may be explained without assuming any physiologic relationship between the age of onset of diabetes in parent and child. The method of analysis used, although independently arrived at by the present authors, was suggested in 1912 by Pearson [8] in a theoretic discussion of antedating in mental illness. We may conclude with him that the difference

in age of onset between the two generations ". . . is not a result or a demonstration of any physiological principle of antedating. . . ." Pearson went on to say that antedating ". . . is solely due to the fact that those who develop the disease at different ages are not equally likely to marry and become parents." It will be shown later that this statement is incorrect, because differential fertility accounts for only a portion of the total frequency of prior onset which is observed clinically.

Variability in age of onset is sufficient in itself to lead to a high frequency of earlier age of onset of a disease in the affected children of affected parents, even when there is no relation between the age of onset in parent and child. This is so because in any symmetric distribution half the values and in any slightly skewed distribution almost half the values are lower than the mean; hence, on the average, 50 per cent of the children would be expected to have onset prior to the parent. If the range of onset coincides in part at least with the reproductive period, the frequency of prior onset may be expected to be increased because the affected individuals who, for one reason or another, do not survive the reproductive period will have fewer children than those who do. Those affected individuals who do not survive the reproductive period will be the ones with earlier age of onset than that of the general population. Consequently, the average age of onset will be higher among affected individuals who are parents than it would be in an unselected population. In the case of diabetes, the affected children of these individuals are such an unselected population. (The average age of onset in the affected parents is 59 years, in their children 48 years, and in the total sample of 1,379 cases, 47 years.) The magnitude and frequency of the effect would depend on how variable the age of onset of the disease is and on how much of the reproductive period is included in this interval. (This argument is an expansion of an essentially similar one offered by Pearson.[8]) Factors such as increased mortality rate, lowered fertility in a portion of the parental generation or earlier detection in the second generation, either because of prior knowledge of the occurrence of the disease in the family or of improved medical technics, or bias in selecting cases, would tend to enhance the observed differences. We may well speculate that this explanation is applicable to many if not all reported instances of "anticipation" in diseases with variable age of onset. At any rate, it most certainly appears to be the explanation in the case of diabetes. Inasmuch as anticipation in diabetes is the result of statistical and not physiologic phenomena, and because the term has come to have a definite physiologic connotation, it would seem desirable to discontinue the use of this term in referring to cases of prior onset of the disease in children of affected parents. The more noncommittal and more descriptive expression "prior onset" is to be preferred.

It is of interest to note that the improved technics of caring for diabetic patients, leading to an increased rate of survival and of successful pregnancies in those with early onset, can be expected to lead to a decrease in the fre-

quency with which prior onset in the child will occur. However, even if the distribution of the age of onset in the parent approaches that of the general population (column 2 of table 2), prior onset in the child will occur more than 40 per cent of the time. The reader will recall that only one of the 200 diabetic parents became diabetic prior to the age of 30 years, and that it was suggested that this is so because individuals of the parent's generation who became diabetic prior to age 30 years became diabetic before the introduction of insulin, and hence did not survive to become parents. The omission from the parental population of those who became diabetic prior to age 30 years accounts for the high frequency of prior onset observed (67.5 per cent), as compared to the approximately 40 per cent which would be expected if there were no differential mortality or fertility among the diabetic patients. Pearson's explanation would account for the excess, but not for the basic frequency of approximately 40 per cent resulting from variability in age of onset. It is for this reason that we cannot accept Pearson's statement that ". . . antedating . . . is *solely* due to the fact that those who develop the disease at different ages are not equally likely to marry and become parents."

In conclusion, we wish to emphasize (1) that prior onset of diabetes in the diabetic children of diabetic parents is observed as frequently as it is at the present time because of three reasons: (a) the age of onset of diabetes is highly variable and includes the reproductive period, (b) nearly all diabetic patients who become parents become diabetic after the age of 30 years, and (c) there is no biologic relation between the age of onset in the parent and in the child; and (2) the age of onset of diabetes in a parent cannot be used to predict the age of onset in the children.

Summary

Two hundred family histories in which the age of onset of diabetes in parent and child were reported were analyzed to examine the validity of the concept of anticipation as a physiologic phenomenon in diabetes. The analysis showed that anticipation is a statistical (that is, numerical) and not a biologic phenomenon. Accurate predictions, based on the assumption that *there is no physiologic relation between the ages of onset in parent and child,* were made of the frequency with which the age of onset would occur in an earlier decade of age in the child than in the parent and of the average difference in age of onset that would be observed in these cases. The predictions agreed with the values obtained from the histories on which this study was based and with those derived from Woodyatt and Spetz's [8] and Harris's [18] studies.

It is shown that the unfavorable uterine environment provided the fetus by diabetic or prediabetic mothers is not a major factor in determining the age of onset in their diabetic offspring.

It is recommended that the term "anticipation" not be used in discussing the observations relating to prior age of onset of diabetes in parent and child, and that it be replaced by the more descriptive expression "prior onset," which does not carry with it any of the physiologic implications of the former term.

It is with pleasure that we record our gratitude to Dr. Joseph Berkson for his many helpful suggestions.

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PROLONGED RENAL SALT WASTAGE IN "LOWER NEPHRON NEPHROSIS" *

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THE separation of the clinical course of "lower nephron nephrosis" [1] into three periods [2, 3, 4] emphasizes not only the therapeutic indications of each period but also serves to indicate certain disturbances in renal function. Thus, in the first period (the period of renal damage), peripheral circulatory failure appears to be the most common antecedent cause of tubular damage,[5, 6] and renal function suffers from the effects of shock.[6] The second period (period of maximal renal insufficiency), lasting usually eight to 14 days, is characterized by failure to clear waste products and failure of regulation of water and electrolyte balance. These disturbances are related to a failure with low urinary output, apparently resulting from a combination of backward diffusion of the glomerular filtrate through the tubules [1, 6, 7, 8, 9, 10] and a lowered renal blood flow.[7] The final period (period of recovery) may be subdivided [11] into a shorter interval of copious diuresis (failure with high urinary output), lasting ordinarily about one week, and a longer interval of renal convalescence, requiring one to six months, during which renal function reverts to its former status.

During the diuresis substantial quantities of water, electrolytes and nitrogenous wastes are excreted, although the urine remains dilute. The concentration of chlorides in the urine may vary markedly in individual cases, such as between 17 and 80 mEq. per liter of urine.[4] The chlorides, representing mainly sodium chloride, reflect the quantity of sodium excreted. Since the daily urinary volume may fluctuate between 6 and 10 L., the varying chloride concentrations represent a diurnal excretion ranging between 100 and 800 mEq. of chloride.† Naturally salt loss of these magnitudes must be replaced, as otherwise extreme grades of sodium chloride and extracellular fluid deficits accrue. Fortunately, in most instances the interval of copious diuresis is followed by a recession in the excretion of chloride to such levels as to preclude the necessity for a prolonged prescribed intake of salt. From this time on, patients ordinarily can maintain their own needs for salt.

The two cases herein reported are of interest since they represent examples of prolonged and excessive chloride excretion during the recovery from "lower nephron nephrosis." The persistent excessive chloride excre-

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† Expressed as grams of NaCl, these quantities represent 6 to 47 gm., or up to nearly 50 per cent of the total normal extracellular quantity of NaCl.

tion, 200 to 800 mEq. per 24 hours, exceeded any formerly encountered [2, 3, 4] and eventuated in temporary intervals of the "syndrome of salt deficiency." [12] The excessive wastage of salt required a persistent vigil for nearly two months, but recovery eventually occurred and has persisted for one and one-half and two years, respectively. In retrospect, it appears unlikely that these two elderly patients, each aged 74 years, would have recovered without the rather aggressive salt régime instituted during the two months. Moreover, since these patients were arteriosclerotic and had arteriosclerotic heart disease, it became necessary to overcome the psychologic hurdle of the customary procedures in the management of cardiac patients in order to institute the vigorous intake of sodium chloride, sodium bicarbonate and potassium chloride necessary to replace that which was lost. We present these cases as special forms of "lower nephron nephrosis" from the functional and therapeutic viewpoints.

Case Reports

Case 1 (*Chart 1*). A 74 year old white male was admitted on February 10, 1950, for a transurethral prostatic resection, the second resection for carcinoma of the prostate gland. On the evening of admission, in preparation for the operation, a blood transfusion was given. The transfusion was discontinued after 225 c.c. because of a reaction which was subsequently determined to be due to incompatible blood. The patient reacted with a chill, fever, transient cyanosis and dyspnea. The pulse was markedly irregular. The entire reaction lasted three hours, during which time there was no evident hypotension. The following day jaundice was evident, and the icterus index was 84. Three days later the icterus index was 15. The blood urea, which prior to the transfusion was 20 mg. per 100 c.c., was 114 mg. per 100 c.c. on the following day. Hemoglobin was detected in the urine. Oliguria developed (525 c.c. urine the first day, 153 c.c. urine the second day). The blood pressure remained near 190/100 mm. of Hg. The patient was placed on a conservative régime aimed primarily at replacing the daily loss of fluid, that is, 1,000 c.c. for insensible loss, plus the volume lost in the urine.[2, 3, 4]

Oliguria was prominent until the eighth day. The total urinary volume during this period was 4,424 c.c., the daily urinary volume being 153 c.c. on the second day and 1,470 c.c. on the eighth day. The urinary specific gravity remained near 1.007. The total fluid intake for this interval was 14,600 c.c., or approximately 1,000 c.c. per day greater than the daily volume of urine. Azotemia reached a maximum of 250 mg. of urea per 100 c.c. Hypochloremia (plasma Cl 72 mEq./L.), hyponatremia (serum Na 130 mEq./L.), and acidosis (plasma HCO_3 18 mEq./L.) were observed. The output of chloride in the urine during this interval was not determined, but it apparently exceeded the intake of 188 mEq., since the hypochloremia was prominent.

Between the ninth and the twelfth days diuresis began, as indicated by the total urinary volume for this interval of 18,745 c.c. The daily urinary volume was elevated from 2,515 c.c. on the ninth day to 6,770 c.c. on the twelfth day. The total fluid intake for the same interval was 22,000 c.c., or 800 c.c. per day greater than the urinary volume. The urinary specific gravity remained near 1.009. This volume of urine contained 1,187 mEq. of chloride (average concentration, 63 mEq./L.). At the same time the intake of sodium chloride was 595 mEq., but to this was added 214 mEq. of sodium bicarbonate. At the end of this interval the plasma chloride concentration was 72 mEq./L., the serum sodium was 136/mEq./L., plasma bicarbonate,

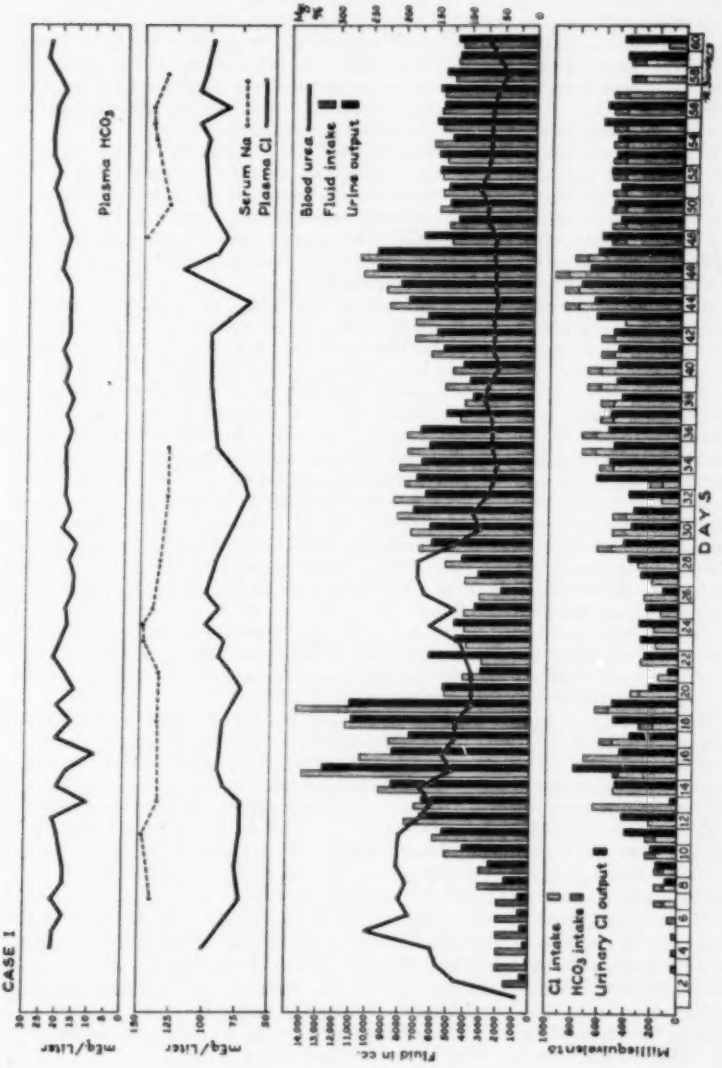
CASE 1
Plasma HCO_3
Serum Na
Plasma Cl
Blood urea
Fluid intake
Urine output
Cl intake
HCO_3 intake
Urinary Cl output
DAYS

CHART 1.

21 mEq./L., and the serum potassium 3.8 mEq./L. The patient was digitalized on the ninth day, and he was given oxygen periodically during the following week.

A critical episode occurred on the twelfth day despite the onset of the recession of the azotemia. The patient became disoriented and irrational. Basal râles were heard. The blood pressure dropped from 220/112 to 180/100 mm. of Hg. Auricular fibrillation appeared and remained throughout most of the hospital stay. Singultus became marked; and periods of cyanosis occurred. This episode was climaxed by the occurrence of brief convulsive seizures and a transient hemiplegia.

It was apparent that a serious deficit of salt (NaCl) had occurred. The measurements indicated a deficit of 592 mEq. Despite the circulatory complications, on the thirteenth day 573 mEq. of sodium chloride and 68 mEq. of potassium chloride were given, mostly by stomach tube. On this day, the urinary volume was 7,090 c.c. but the chloride excretion dropped to 55 mEq. The patient improved markedly, the main residuum being transient disorientation. Mild diarrhea occurred between the thirteenth and fifteenth days but did not recur thereafter.

Between the fourteenth and the twentieth days the total urinary volume was 64,880 c.c., reaching a daily maximum of 12,750 c.c. on the fifteenth day. The total fluid intake for the same period was 73,600 c.c., or a daily average of 1,200 c.c. in excess of the urinary volume. By now the intake included a daily average of 860 c.c. of orange juice and 500 c.c. of Protenum.* The total urinary chloride excretion was 3,824 mEq. (average concentration, 50 mEq./L.), whereas the known intake of salt amounted to 2,905 mEq. of sodium chloride, 383 mEq. of sodium bicarbonate and 270 mEq. of potassium chloride. The plasma chloride concentration was elevated to 90 mEq./L., the serum sodium concentration remained near 136 mEq./L., the plasma bicarbonate concentration fluctuated between 10 and 20 mEq./L., and the serum potassium concentration remained near 5 mEq./L. Throughout this period there were bouts of disorientation, but at the end of this interval the patient was quiet and well oriented and conversed rationally. On the fourteenth and again on the eighteenth days the patient received 500 c.c. of blood. The peripheral hemoglobin was elevated from 9.4 to 11 gm. per 100 c.c. of blood.

The increased intake of chlorides was associated with a greater urinary excretion of this ion, as revealed by a total daily chloride excretion varying between 350 and 790 mEq. Accordingly, it was decided to determine whether the excessive excretion resulted primarily from the enhanced intake.

Between the twenty-first and the twenty-eighth days the total known chloride intake was 1,737 mEq. (1,078 as NaCl, and 659 as KCl), while during the same interval the total urinary chloride excretion was 1,992 mEq. The total urinary volume for this period decreased, amounting to 31,790 c.c.; thus, the average urinary chloride concentration remained near 62 mEq./L. The total fluid intake for this period was 30,100 c.c., and included an average of 2,000 c.c. of orange juice and 500 c.c. of Protenum® per day. This period was associated not only with a salt deficit but also with water deficit, as the intake did not provide for the daily insensible loss. The deficit of water and salt was attended by an elevation in the blood urea concentration from 92 to 190 mg. per 100 c.c. At the same time the plasma chloride concentration was transiently elevated to 100 mEq./L., the serum sodium to 141 mEq./L., and the serum potassium to 6.1 mEq./L., while the plasma bicarbonate concentration remained between 15 and 17 mEq./L. Events during the next six days revealed that these increases in plasma ionic concentration apparently were the result of the water deficit, as the replacement of this deficit was attended by a prominent dilution of all ions. The acidosis was not relieved as expected in dehydration.

* Protenum® (Mead-Johnson) as prepared contained approximately 1 calorie per cubic centimeter and a negligible amount of salt.

The interval described in the foregoing paragraph demonstrated that the excessive wastage of chloride via the urine, amounting to 350 to 800 mEq. per day on previous days, was not just a function of a stepped-up intake, as with a lowered intake the daily excretion was still in the range of 250 to 384 mEq. per day, or quantities sufficient to effect a deficit. Clinically, the patient's status varied between quiet interludes and periods when he was restless and irrational. The blood pressure remained near 160/90 mm. of Hg, the pulse near 100.

Between the twenty-ninth and thirty-fourth days the total urinary volume was 40,290 c.c., while the intake was 47,280 c.c., or 1,300 c.c. per day in excess of the urinary output. The intake included an average of 1,300 c.c. of orange juice and 430 c.c. of Protenum® per day. In addition, blood transfusion of 500 c.c. was given on the thirty-second day. The total urinary chloride excretion was measured as 2,706 mEq., for a daily average concentration of 67.5 mEq./L. The salt intake consisted of 1,926 mEq. of sodium chloride, 216 mEq. of potassium chloride and 418 mEq. of sodium bicarbonate. On this régime the blood urea receded to 56 mg. per 100 c.c. However, hypochloremia became prominent once more (plasma Cl 70 mEq./L.), hyponatremia recurred (serum Na 130 mEq./L.), and acidosis persisted (plasma HCO_3 18 mEq./L.). The serum potassium concentration was near 4 mEq./L. At the height of the hypochloremia the patient became very restless and irrational, and the blood pressure dropped to 110/70 mm. of Hg.

During the above interval the chloride deficit continued to accrue. On two days (the thirty-second and thirty-third), the urinary chloride excretion far exceeded the intake. The overall increment in chloride intake was associated with a greater urinary excretion, which varied between 350 and 634 mEq. per 24 hours. Thus, renal salt wastage continued despite an adequate excretion of nitrogenous waste products.

The interval between the thirty-fifth and forty-third days was associated with a total chloride excretion of 5,235 mEq. The intake contained 4,516 mEq. of sodium chloride, 972 mEq. of potassium chloride, 861 mEq. of sodium bicarbonate, and a daily average of 1,700 c.c. of orange juice and 480 c.c. of Protenum. The urinary volume amounted to 48,750 c.c., while the intake was 55,460 c.c. Clinically there was marked improvement. The blood pressure was elevated to 160/90 mm. of Hg. The patient became rational and ambulatory, and for the first time began partaking of a general diet. The plasma chloride concentration was elevated to 97 mEq./L.

A final bout of hypochloremia became pronounced on the forty-fourth day. The plasma chloride concentration was receding toward the end of the above period and dropped to a low of 72 mEq./L. This was soon circumvented by increasing the intake of salt. From the forty-eighth day on, the plasma chloride concentration was maintained near 100 mEq./L., the serum sodium concentration was 140 mEq./L., the plasma bicarbonate concentration was 24 mEq./L., and the serum potassium concentration remained in the vicinity of 5 mEq./L. The daily urinary chloride excretion varied between 400 and 700 mEq. per day until the sixtieth day. Thereafter, it receded to 100 to 230 mEq. daily. The patient was discharged on the seventy-second day after the onset of the acute renal failure without a prescribed salt intake. The temperature was periodically elevated to 100° F. until the fortieth day. Between the twentieth and thirtieth days penicillin (50,000 units every six hours) was given. Between the thirtieth and sixtieth days aureomycin (1 to 2 gm. daily) was given. The temperature became normal on the fortieth day. Vitamin B was given throughout the hospital course.

On discharge the phenolsulfonphthalein test was 26 per cent of normal and the urea clearance test was 20 per cent of normal. The urinary specific gravity was 1.010. The patient has remained well from the standpoint of renal function for one and one-half years.

Case 2 (*Chart 2*). A 74 year old white male was admitted with symptoms of

prostatic enlargement, which included moderate dribbling of urine, frequency during the day and night, decreased force of the urinary stream, difficulty in initiating the stream and inability to empty the urinary bladder. Two years before, an episode of acute urinary retention had subsided without operative intervention. The physical examination revealed peripheral arteriosclerosis; blood pressure, 190/94 mm. of Hg; pulse, 80, and respirations, 20. The prostate gland was enlarged, but otherwise the physical findings were normal. An electrocardiographic tracing indicated myocardial damage (ST-T changes, abnormal precordial leads, frequent ventricular extrasystoles). The blood urea was 24 mg. per 100 c.c. A urinalysis revealed a specific gravity of 1.022, and negative chemical and microscopic findings.

On June 3, 1949, a transurethral prostatectomy was performed, 21 gm. of tissue being removed. The microscopic diagnosis was adenomatous hyperplasia of prostate gland. For 19 hours prior to the operation the patient received seven doses of quinidine orally, a total of 2 gm. During the operation, which was conducted under spinal anesthesia (150 mg. novocain with adrenalin), the blood pressure remained near 160/90 mm. of Hg, and the pulse rate was 70. Following the operation, the urinary bladder was irrigated continuously with water. The patient was conscious, but the blood pressure dropped to 118/70 mm. of Hg. Six hours later the patient became disoriented, periods of excitement alternating with a stuporous state. At this time the blood pressure was 100/70 mm. of Hg. Quinidine was discontinued. The blood pressure remained near 100/70 mm. of Hg for six additional hours but was elevated to 170/90 mm. of Hg after 500 c.c. of blood. The following day the patient was jaundiced (icterus index, 27) and oliguric, and the blood urea concentration was 185 mg. per 100 c.c. Several bouts of vomiting occurred. The blood pressure remained at a sustained level of 200/90 mm. of Hg.

With the recognition of the acute renal failure, the patient was placed on a conservative régime consisting mainly of an attempt to maintain the intake of water and sodium chloride comparable to the estimated loss. In addition, 300,000 units of penicillin were given daily. The patient took negligible quantities of nourishment. Oliguria persisted for 10 days, during which time the total urinary volume was 9,930 c.c., having increased gradually from 330 c.c. on the first day to nearly 2,000 c.c. on the ninth and tenth days. The urinary specific gravity remained between 1.005 and 1.007. The azotemia reached a maximum of 280 mg. per 100 c.c. of blood urea, the plasma bicarbonate concentration was approximately 15 mEq./L., and a moderate hypochloremia (plasma chloride, 80–86 mEq./L.), and hyponatremia (serum Na 132–136 mEq./L.) developed. The serum potassium concentration was 5 mEq./L. The total intake through the tenth day amounted to 27,500 c.c. of water and 1,500 mEq. of sodium chloride. According to two measurements, the urinary chloride concentration was 50 mEq./L. The environment was hot and humid, and active sweating occurred. The average daily fluid intake exceeded the urinary output by 1,700 c.c. Intervals of restlessness and irritability occurred, but for the most part the patient was oriented and coöperative. Although the chloride loss by sweating and the short period of irrigation of the bladder was not known, it appeared unlikely that a substantial deficit accrued in view of the intake of 1,500 mEq.

Between the eleventh and twentieth days, progress toward renal recovery occurred. Nevertheless, periods of marked restlessness and irritability ensued. The total urinary volume for this interval was 33,790 c.c., increasing from 3,670 c.c. on the eleventh day to 4,030 c.c. and 5,420 c.c. on the nineteenth and twentieth days. The urinary specific gravity varied between 1.005 and 1.010. The blood urea concentration receded to 110 mg. per 100 c.c. The plasma bicarbonate concentration was elevated to 24 mEq./L., and the plasma chloride and serum sodium concentrations were elevated to 100 and 140 mEq./L., respectively. The serum potassium concentration remained approximately 5 mEq./L. The urinary chloride concentration

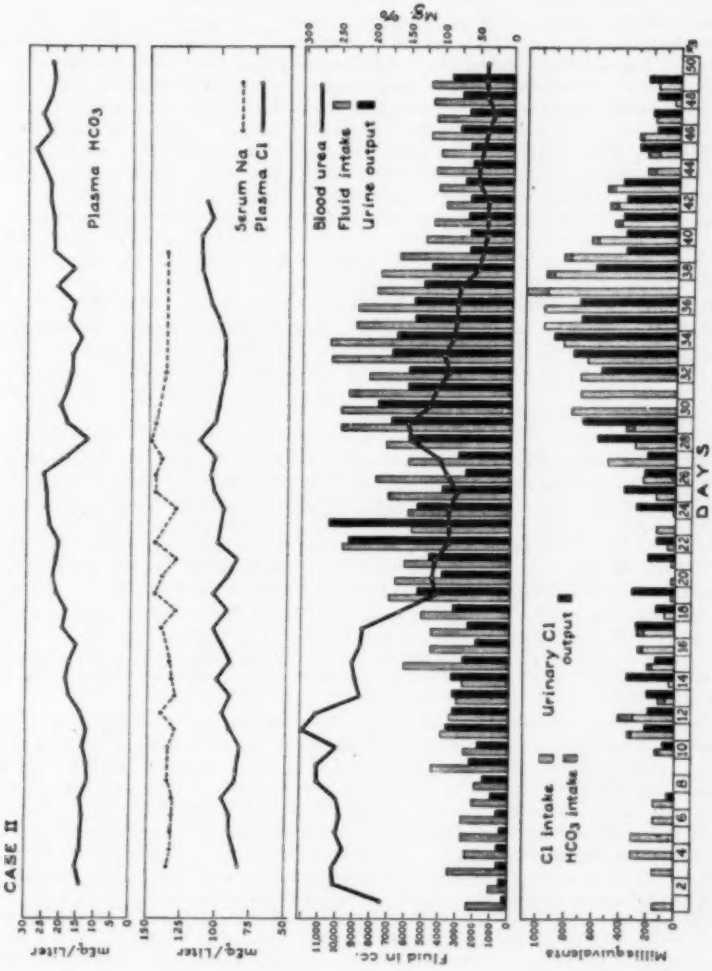
CASE II
Plasma HCO_3
Serum Na
Plasma Cl
Blood urea
Fluid intake
Urine output
Cl intake
HCO_3 intake
Urinary Cl output
DAYS
mEq./Liter
Fluid in cc.
Milliequivalents
% N_2

CHART 2.

varied between 60 and 100 mEq./L., while the total daily urinary chloride excretion fluctuated between 100 and 350 mEq. The measured total renal excretion of chloride was 1,890 mEq. Mild sweating persisted. The known intake of chloride consisted of 900 mEq. of sodium chloride and 270 mEq. of potassium chloride. In addition, the patient was given 325 mEq. of sodium bicarbonate. The over-all fluid intake was 47,800 c.c., or an average of 1,400 c.c. per day in excess of the urinary volume. This fluid intake consisted of water, an average per day of 1,300 c.c. of orange juice and 850 c.c. of a high caloric milk formula, and 6 L. of 10 per cent dextrose intravenously. The fluids were given through an indwelling stomach tube in small quantities throughout the 24 hours. On each of five days the patient was given the red blood cells from 500 c.c. of blood, and the hemoglobin concentration rose from 7.0 to 12.6 gm. per 100 c.c. of blood. Although the exact state of the salt balance was not known, the available estimate suggested a moderate deficit of sodium chloride. Clinically, the patient was restless and irritable periodically. Paraldehyde (4 to 8 c.c. intramuscularly) was given for the restlessness. When quiet, the patient was up in a chair. On the thirteenth day there occurred an interval of dyspnea, restlessness and slight cyanosis. Slight pedal edema was noted. On the fifteenth day the patient was digitalized (digitoxin) and given oxygen periodically.

The next 10 day interval (the twenty-first to thirtieth days) was initiated by a chill, fever (104° F.) and transient cyanosis on the twenty-first day. Cultures of the urine yielded growth of *Aerobacter aerogenes*. Streptomycin (0.5 gm. every six hours) effected a recession of the temperature to 100° F., but another chill occurred on the twenty-fourth day. Following aureomycin therapy, the temperature receded to normal by the thirtieth day.

During this third 10 day interval the total urinary output was 60,475 c.c., reaching a daily maximum of 10,300 c.c. on the twenty-third day. The urinary specific gravity remained near 1.006. The total fluid intake was 78,900 c.c., an average of 7,890 c.c. per day and a daily excess over the urinary volume averaging 1,840 c.c. The fluid intake included a daily average of 1,500 c.c. of orange juice and 1,500 c.c. of a high caloric milk formula. The urinary chloride concentration was about 100 mEq./L., and the total daily chloride excretion varied between 125 and 700 mEq. The increment of chloride excretion became apparent on the twenty-fifth day. At this time the azotemia, which had been abating steadily, was accentuated (blood urea, 145 mg. per 100 c.c.), and acidosis (plasma HCO_3 13 mEq./L.) reappeared. The serum sodium (141 mEq./L.) and plasma chloride (100 mEq./L.) concentrations, however, remained normal. The serum potassium concentration varied between 4 and 5 mEq./L.

The patient continued to exhibit periods of restlessness during which he was disoriented and confused. The pedal edema became pronounced, although pulmonary edema and edema elsewhere were not detected. He was up in a wheelchair for short intervals and on a few occasions walked for short distances. An accurate evaluation of the sodium and chloride balance was not possible. From the known over-all urinary excretion and the known intake of sodium chloride, sodium bicarbonate and potassium chloride and the intake of fruit juice and milk, it was apparent that a moderate deficit of sodium chloride existed despite the pedal edema. Accordingly, during the following 10 day interval the salt intake was increased.

Between the thirty-first and fortieth days 6,930 mEq. of sodium chloride were given. There was an additional intake of 470 mEq. of sodium bicarbonate and 1,080 mEq. of potassium chloride. The urinary chloride concentration varied between 70 and 110 mEq./L. Since the diuresis persisted during this period, the total daily urinary chloride excretion varied between 500 and 850 mEq. Thus, an extreme grade of chloride wastage occurred at this time. The wastage was partly associated with the increased intake in an attempt to replace the apparent deficit.

During this fourth 10 day interval the daily fluid intake exceeded the urinary volume by an average of 3,000 c.c. An accurate estimate of the chloride balance was not available, since the quantities lost by sweating and the amount introduced in the milk and fruit juice were not known. The estimates available, based on general figures, indicated a positive chloride balance for the first time since the onset of the renal failure. During this period the patient improved markedly. The blood urea level dropped below 50 mg. per 100 c.c. The hypochloremia and acidosis, which had recurred, abated. The patient became ambulatory and expressed a desire to go home; soon he insisted on being allowed to return to his home.

The final 10 day interval (the forty-first to fiftieth days) was attended by a recession of the daily urinary volume to 2,500 to 3,000 c.c. The daily urinary chloride excretion receded from 400 mEq. to 200 mEq. on the forty-fourth day. The urinary specific gravity, however, remained between 1.007 and 1.014. A prescribed sodium chloride intake was maintained until the discharge from the hospital on the fiftieth day. Subsequently the patient has taken care of his own requirements and has remained well for two years.

Discussion

It is becoming apparent that the entity described by Lucke [1] as "lower nephron nephrosis" is associated with several clinical variants. This nephropathy has as its basic pathologic defect tubular damage and tubular dysfunction. The most common type observed morphologically reveals a greater degree of damage to the distal segment of the nephron, thus the term "lower nephron nephrosis." Clinically it is possible to distinguish between mild, moderate and severe grades of acute renal failure. Thus, cases entering into the recovery phase, that is, the phase of diuresis, within one week might be considered as mild to moderate cases. The clinical type entering into the diuresis after one to two weeks can be considered as the more severe clinical forms. The most severe clinical variant enters into a state of progressive, unrelenting renal failure,[12] and succumbs in uremia with meager or no signs of renal recovery. Ten to 20 or even more days may elapse before death supervenes in this latter type, depending on the complications and the type of management, as discussed in a separate report.[13]

When one considers all clinical types of acute renal failure apparently due to tubular damage that one observes in a general hospital when the conservative régime of management is instituted, approximately 80 per cent of the patients recover. Under similar conditions, when one deletes the mild to moderate cases, approximately 66 per cent of the patients recover. In the former group, of the 20 per cent that succumb, approximately half of these patients reveal at autopsy such serious complications as massive pulmonary thromboembolism or massive pulmonary fat embolism, or a widespread basic disease, such as miliary tuberculosis or carcinomatosis. The remaining 10 per cent in the fatal group appear to succumb to pure uremia and clinically display the "syndrome of progressive, unrelenting renal failure." This final group morphologically displays not only serious damage to the distal tubular segment but also serious damage to the proximal segment. We prefer to emphasize the tubular damage by using the term "combined upper and lower nephron nephrosis" for this group.[13]

In this present paper we wish to emphasize still another clinical variant of the syndrome of "lower nephron nephrosis." This variant, as the herein presented clinical protocols indicate, is attended by a prolonged period of salt wastage by the kidneys. Should the data presented be verified by other similar observations, it would seem that this complication of the recovery phase is itself recoverable, but that about two months are required for ultimate recovery to occur. During this extended period a close vigil of the salt balance is required, as otherwise serious grades of the "syndrome of salt deficit" occur.

Both of the patients were elderly males with generalized arteriosclerosis and evidence of myocardial disease. The first patient received an incompatible blood transfusion, and the second patient exhibited a prolonged interval of shock and became jaundiced following a blood transfusion, although an incompatibility was not demonstrated. This background, plus the sudden onset of acute renal failure, indicated the existence of "lower nephron nephrosis." Subsequent events were in keeping with a severe grade of renal insufficiency, as the phase of diuresis began between the tenth and the twelfth days of renal failure. Although hypochloremia and acidosis were prominent by this time, the clinical appearance was satisfactory and recovery appeared to be ensuing as the azotemia began to recede.

The first patient exhibited manifestations of the type ascribed to the syndrome of salt deficit on the twelfth day. This interpretation appeared to be verified by the marked improvement following a high sodium chloride intake. The elevated chloride intake accentuated the renal chloride excretion. While a subsequent decrease in the chloride intake was accompanied by a recession in the renal excretion, the excretion was sufficient to effect a deficit. It became apparent that a very high intake was necessary to establish a positive balance in order to cope with the existing deficit. This situation pertained until the sixtieth day after the onset of the renal failure. At this time the chloride excretion, which had varied between 400 and 700 mEq. daily (24 to 42 gm. of NaCl), dropped to 100 to 230 mEq. per day (6 to 13.8 gm. of NaCl). The patient could cope with the latter quantities without a prescribed salt intake.

The second patient revealed evidence of an excessive chloride excretion at the time that a urinary tract infection was detected. The excessive excretion, however, persisted until the forty-third day following the onset of the renal failure. At this time the excretion receded from 400 to 800 mEq. per day (24 to 48 gm. of NaCl) to 200 mEq. (12 gm. of NaCl).

These patients posed nutritional problems, which were met by the administration of liquid nourishment throughout the 24 hour period by means of an indwelling stomach tube. Fruit juices and a high caloric formula were used for nourishment. Potassium chloride and sodium bicarbonate were given along with the sodium chloride.

Although strict balance studies were not conducted, the salt wastage was

demonstrated. The figures given in the text for the chloride intake represented the known amounts given as sodium chloride and potassium chloride. Additional amounts were received by the patient in the liquid nourishment, as orange juice and milk formula. The true chloride deficits were not known, but the need for a high intake was demonstrated by the measurements of the urinary excretion. It appears unlikely that these patients with evident myocardial involvement would have tolerated such high intakes of the various salts given had not the measured excretion approximated that actually lost.

Summary

An additional variant of the syndrome of "lower nephron nephrosis" has been described by the presentation of two case reports involving two elderly patients. This variant is characterized by a prolonged interval of sodium and chloride wastage via the urine. The magnitude of daily total renal chloride excretion varied between 350 and 800 mEq. (20 to 48 gm. of NaCl).

The excessive renal wastage of salt lasted for 60 and 44 days, respectively, after the onset of the acute renal failure. During this period a high intake of salt (NaCl, KCl and $NaHCO_3$) appeared necessary, despite the evidence of myocardial insufficiency. The disturbance leading to salt wastage was itself recoverable, as demonstrated by a state of well-being which has lasted one and one-half and two years, respectively.

Both patients posed a nutritional problem which was handled by means of liquid nourishment given through an indwelling gastric tube.

The possibility of this type of complication should be considered in patients recovering from "lower nephron nephrosis."

Acknowledgment

The authors are grateful to Dr. W. Grady Reddick and Dr. Karl King for the opportunity to observe these patients and to use the material in this report. These patients were under the care and management of Dr. W. Grady Reddick, of Dallas.

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CASE REPORTS

THE RECOVERY OF STREPTOMYCIN-SENSITIVE TUBERCLE BACILLI FROM A PATIENT WITH PULMONARY TUBERCULOSIS WHO HAD PREVIOUSLY YIELDED HIGHLY RESISTANT BACILLI *

By Roger S. Mitchell, M.D., Emanuel Wolinsky, M.D., and William Steenken, Jr., *Trudeau, N. Y.*

The appearance of streptomycin-resistant tubercle bacilli in the sputum of streptomycin-treated patients with pulmonary tuberculosis has been repeatedly found to coincide with a loss of clinical effectiveness of the drug. Tubercle bacilli exhibiting streptomycin sensitivity, as well as others with different degrees of streptomycin resistance, have occasionally been recovered from one or more lesions in the same patient, both at post mortem,[1-6] and from surgically resected lung tissue.[1, 7] There is no published evidence to date that highly streptomycin-resistant tubercle bacilli may become streptomycin-sensitive after repeated in vitro passage in culture media both with and without streptomycin. Serial animal passage of streptomycin-resistant organisms has also failed to yield streptomycin-sensitive strains.[8]

Fisher reported in 1948 an apparent reversion to streptomycin sensitivity of the tubercle bacilli recovered from six patients who had previously yielded strains of low-grade streptomycin resistance.[9] Ferebee and Appel made the same observation in 18 per cent of 99 patients whose bacilli had shown various degrees of streptomycin resistance; after 120 days of streptomycin treatment, there were only 46 patients whose bacilli were highly streptomycin-resistant (to 100 mcgm. of streptomycin or more per ml. of medium); four (9 per cent) of these yielded only streptomycin-sensitive bacilli during the latter part of a year's observation without treatment.[10] Karlson et al. made similar observations in five of eight patients whose bacilli had shown resistance to 10 mcgm. of streptomycin or more per ml. of medium during treatment with streptomycin and PAS on three days of each week for from three to eight months [11]; in two of these, the reversion occurred while the patients were still on treatment. No adequate explanation of this apparent change has yet been offered.

In the case to be presented, a change from high streptomycin resistance* to complete streptomycin sensitivity of tubercle bacilli recovered from the sputum seems also to have occurred. From a careful appraisal of the four year clinical course, however, there is an interpretation of this event which is not contrary to the established in vitro behavior of streptomycin-resistant tubercle bacilli and which may have clinical application.

* Received for publication January 9, 1952.

From Trudeau Sanatorium, and The Trudeau Laboratory of The Trudeau Foundation for the Clinical and Experimental Study of Pulmonary Disease, Trudeau, New York.

Case Report

A 26 year old single white female hairdresser was admitted to Trudeau Sanatorium with far advanced pulmonary tuberculosis on October 13, 1948, complaining of cough, expectoration and weakness. She had been well until January, 1947, when she noted frequent "colds" and easy fatigability. Bilateral cavitary pulmonary tuberculosis was diagnosed in August, 1947 (figure 1), by chest roentgenogram and sputum examination.

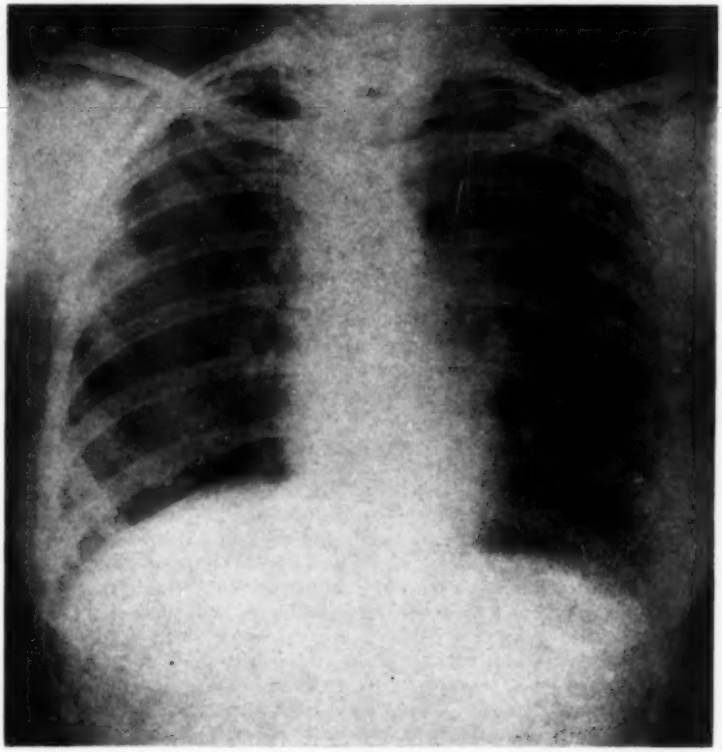

Fig. 1. Chest roentgenogram taken August 19, 1947, showing cavities at the right apex, right base and left root.

She came at once to Saranac Lake, where she was given moderately strict bedrest in a nursing cottage. There was some immediate improvement, but seven months after her arrival there was an increase of infiltration bilaterally. As a consequence, 1 gm. of streptomycin was given intramuscularly daily for 73 days, from May 10, 1948, to July 21, 1948. There was prompt clinical and roentgenographic improvement, including disappearance of the cavity at the right base. From a sputum culture obtained on June 7, 1948, tubercle bacilli were found to be completely

streptomycin-sensitive, as they had been since the first test made on sputum obtained two days after beginning of streptomycin treatment.

A sputum obtained on June 14, 1948, 35 days after beginning streptomycin treatment, contained tubercle bacilli which were able to grow in Tween-albumin liquid medium containing 1.000 micrograms of streptomycin/ml. Coincident with this development, there was increase in cough and expectoration, increase in the size of the cavity on the left, and increase in the Gaffky count.

On admission to Trudeau Sanatorium on October 13, 1948, the patient was a

TABLE I

Range of All Tests of in Vitro Sensitivity to Streptomycin and PAS of Tubercle Bacilli Isolated from Cultures of the Patient's Sputum (S) or Gastric Washings (G), Correlated with Dates of Chemotherapy and Clinical Events

Dates	Source of Tubercle Bacilli	In Vitro Drug Sensitivity			Chemotherapy	Major Clinical Events
		Streptomycin		PAS ‡		
		Direct Test on Solid Medium*	Subculture Test in Liquid Medium†			
8-10-47						Began rest treatment in Saranac Lake.
3- 5-48						Bilateral increase of infiltration.
5-10-48					Streptomycin 1 gm. daily	
5-12-48	S	Sens.	0.5	—		
5-24-48	S	Sens.	0.5	—		
5-31-48	S	Sens.	2.5	—		
6- 7-48	S	Sens.	0.5	—		Cavity at right base disappeared.
6-14-48	S	Mod. Res.	>1000	—		
6-21-48	S	Mod. Res.	>1000	—		Increase in size of cavity and spread of infiltration on left.
6-28-48	S	High Res.	>1000	—		
7- 5-48	S	Sl. Res.	5.0	—		
7-21-48	S	Sens.	2.5	—		
10-13-48						Admission to Trudeau Sanatorium.
10-18-48	S	High Res.	>1000	—		
11-19-48	S	—	>1000	Sens.		Pneumoperitoneum started.
12-10-48	S	Mod. Res.	2.5	—		
1-19-49	S	High Res.	>1000	—		
3-21-49	S	High Res.	—	Sens.	PAS, 10 gm. daily	Increase in size of cavity and spread of infiltration on left.
4-11-49	S	High Res.	>1000	Sens.		
4-25-49	S	High Res.	—	—		
5-11-49	S	High Res.	—	Sens.		
5-23-49	S	Culture Negative				
6- 6-49	S	—	>1000	Sens.		
6-20-49	S	—	—	Sens.		
7- 5-49	S	High Res.	—	Sens.		
7-20-49	S	—	—	Sens.		
8-29-49	S	—	>1000	Sens.		
9-19-49	S	High Res.	>1000	—		Increase in size of cavity and spread of infiltration on left.

TABLE I—*Continued*

Dates	Source of Tubercle Bacilli	In Vitro Drug Sensitivity			Chemotherapy	Major Clinical Events
		Streptomycin		PAS ‡		
		Direct Test on Solid Medium*	Subculture Test in Liquid Medium†			
9–29–49						
10–10–49	S	Culture Negative				
10–24–49	S	—	—	Sens.		
11– 7–49	S	—	—	Mod.		
11–21–49	S	—	—	High		
12– 5–49	S	—	—	Sens.	PAS, 12 gm. daily	
12–19–49	S	—	—	Sl.		Increase in size of cavity and spread of infiltration on left.
1– 3–50	S	High Res.	>1000	Sl.		
1–16–50	S	—	—	High		Left phreniclasis.
1–29–50	S	High Res.	>1000	—		
2–27–50	S	—	—	Mod.		
3–20–50	S	—	—	Sens.		Cavity on left disappeared.
5–19–50	S	Sens.	0.5	Sens.		
7–12–50	S	Sens.	0.5	Sens.		
9–20–50	S	Sens.	—	Sens.		
10–16–50	S	Sens.	—	—		
12– 6–50	S	Sens.	0.5	Sens.		
1– 5–51	S	Sens.	0.5	Sens.	Streptomycin, 1 gm., and PAS, 12 gm. per day	
1–19–51	S	Sens.	0.5	Sens.		Cavity at right apex disappeared.
2– 7–51	S	Culture Negative				
3– 7–51	S	Culture Negative				
4– 6–51	S	Culture Negative				
4– 9–51	S	Culture Negative				
4–13–51	S	Culture Negative			Streptomycin, 1 gm. twice weekly, and PAS, 12 gm. per day continued to present	
4–27–51	G	Culture Negative				
4–30–51	G	Culture Negative				
5– 4–51	S	Culture Negative				
8– 8–51	S	Culture Contaminated				
8–12–51	S	Culture Negative				
8–15–51	S	Culture Negative				

* Concentrate of material planted directly on tubes of A.T.S. solid medium containing approximately 3.5, 20 and 250 micrograms of streptomycin/ml. of medium. Evaluation of sensitivity made by comparing the speed of appearance and amount of growth on the streptomycin tubes with controls.

† Representative sample of growth from original culture on solid medium transferred to Tween-albumin liquid medium and resultant growth tested in same medium containing approximately 2-fold dilutions of streptomycin from 1,000 to 0.5 micrograms/ml. of medium. Figures in column indicate minimal concentration of streptomycin necessary to inhibit growth.

‡ PAS tests done on solid medium, both direct and subculture.

Dash (—) = Test not made. Sl = Slightly resistant. Mod. = Moderately resistant. High = Highly resistant.

thin, chronically ill appearing but cheerful young woman with a severe cough, a normal temperature, pulse of 72–96, many râles in the right lung, and an otherwise essentially negative physical examination. Pneumoperitoneum was induced on November 19, 1948. During the period from June, 1948, to February, 1950, the patient's pulmonary tuberculosis remained very unstable. This instability, however, was confined almost exclusively to the left lung, where there were three separate

episodes of sudden enlargement of the cavity, and increase of shadowing in the adjacent lung (see table 1), with coincident aggravation of symptoms. Meanwhile, the right apical cavity became smaller and the infiltration showed some clearing and contraction throughout the right lung.

Two 120-day courses of PAS, 10 to 12 gm. per day by mouth, were given from March 19 to July 17, 1949, and from September 29, 1949, to January 26, 1950.

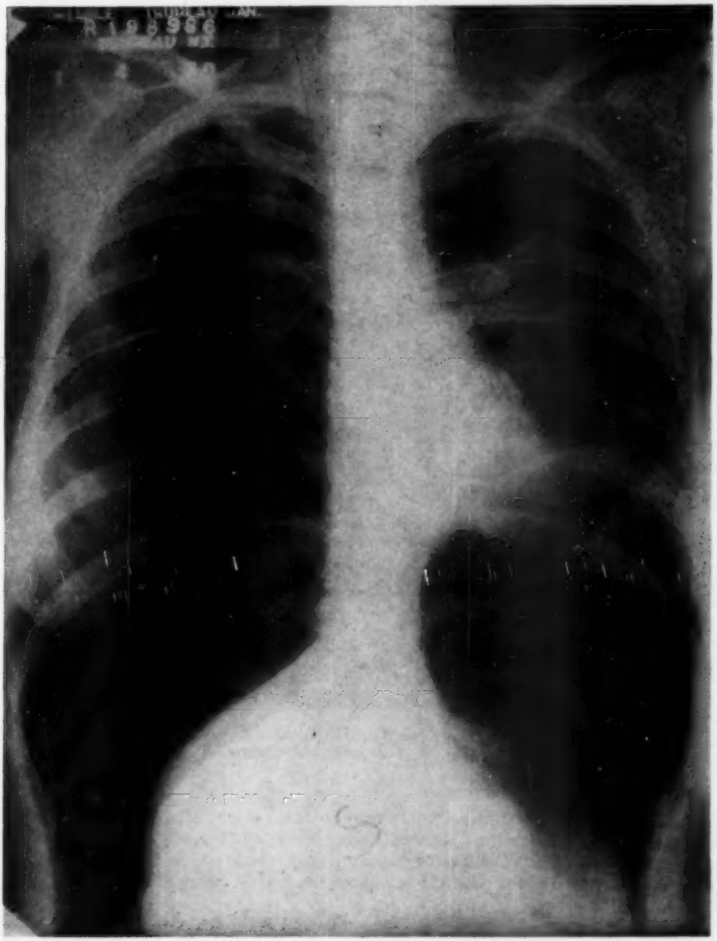

FIG. 2. Chest roentgenogram taken January 4, 1950, showing a recent reactivation of disease and enlargement of cavity at the left root. Cavity still present at right apex. Pneumoperitoneum.

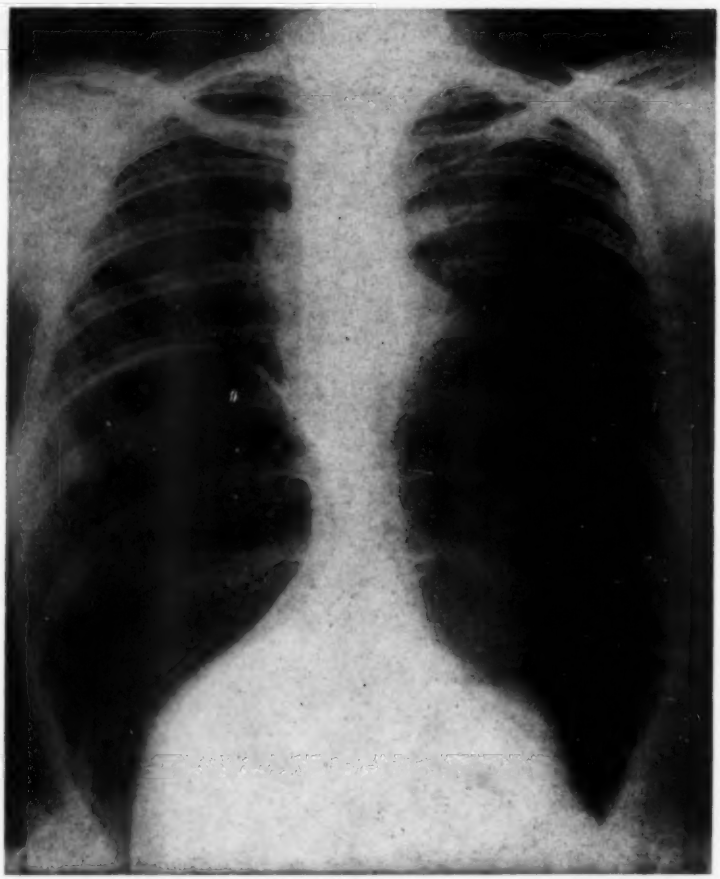

FIG. 3. Chest roentgenogram taken April 3, 1950, showing prompt clearing and disappearance of cavity at the left root following left phreniclasis. Cavity still present at right apex.

Tubercle bacilli recovered from sputum were completely sensitive to PAS before PAS treatment, and remained so until November 7, 1949, about one month after the second course of PAS was started; at this time, moderate resistance to PAS was noted. This in vitro PAS resistance persisted on frequent examinations through February, 1950.

Because of the continuing instability of disease in the left lung (figure 2), a left phreniclasis was added to the pneumoperitoneum on January 21, 1950. This was followed by a considerable reduction in the size of the left lung, clearing of infiltration, and prompt disappearance of cavity by both stereoscopic (figure 3) and

planigraphic films. The highly streptomycin-resistant organisms, which had been fairly consistently recovered for 20 months, organisms which had also been PAS-resistant since October 24, 1949, abruptly disappeared from the patient's sputum (table 1). Organisms recovered now showed complete sensitivity to both streptomycin and PAS which persisted until the cultures became negative in February, 1951.

As a consequence of this rather unusual development, combined daily streptomycin and PAS were given, beginning December 14, 1950, and have been continued to the present time. The only remaining cavity—that in the right apex—disappeared in January, 1951; sputum and gastric washing cultures were then repeatedly negative from February 1, 1951, to the date of this report. The patient has done well, both roentgenographically (figure 4) and symptomatically, and is now ambulant.

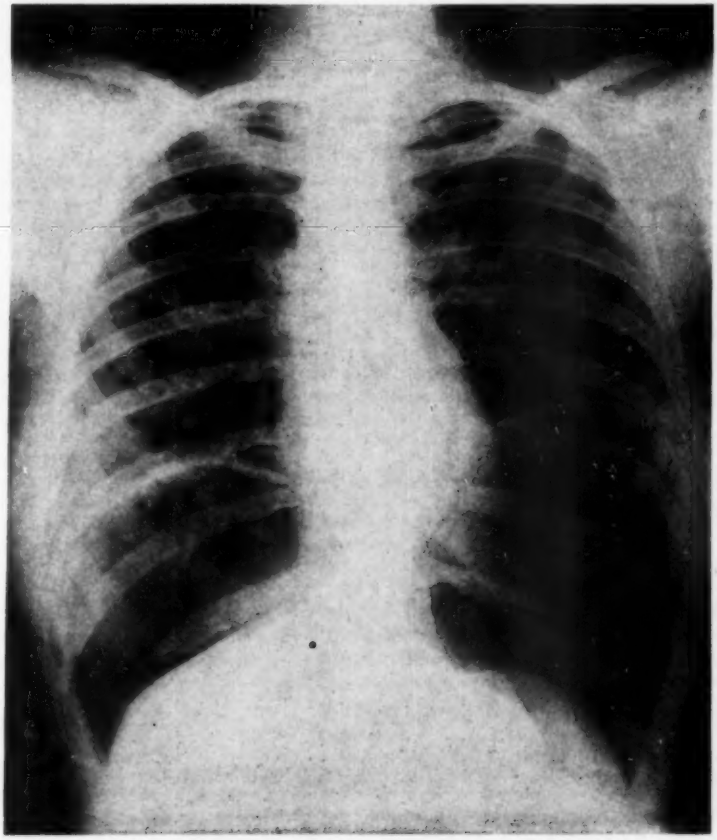

FIG. 4. Chest roentgenogram taken October 22, 1951, showing disappearance of all cavities and control of disease in both lungs 10 months after beginning retreatment with combined streptomycin-PAS.

Comment

From these data, one may postulate that the tubercle bacilli in the left lung cavity were highly streptomycin-resistant at the same time that those in the right lung cavity were streptomycin-sensitive.

The three relatively sensitive cultures in July and December, 1948, interspersed with the many highly resistant cultures during a 20-month period, represent a phenomenon which is occasionally seen when frequent tests are made; there is no satisfactory explanation.

A search through the streptomycin-sensitivity files of the Trudeau Laboratory was made for other instances of a similar nature. Out of approximately 800 cases studied in five years, five additional cases (0.75 per cent in all) were found in which streptomycin-resistant tubercle bacilli from cultures of sputum were replaced by streptomycin-sensitive organisms. The findings in two of these five cases have already been described.[12] In only two of these cases were the bacilli highly resistant (to 1,000 micrograms of streptomycin or more/ml. of medium):

(1) *V. S.* This patient had bilateral cavities when streptomycin was first given which persisted for one year after streptomycin resistance appeared; all cavities then disappeared following induction of unilateral pneumothorax; no bacilli were studied for streptomycin sensitivity for the next three years but, when finally studied, the organisms were completely sensitive and cavities were still not visualized in either lung.

(2) *A. S.* yielded bacilli which were completely sensitive after being highly resistant, with a one-year hiatus between tests; no cavity was ever discovered in either lung at any time.

The cultures from three patients exhibited moderate streptomycin resistance (to 30, 60 and 125 micrograms of streptomycin/ml. of medium, respectively), and later yielded completely sensitive organisms:

(1) *M. McC.* did so immediately following a thoracoplasty and the disappearance of the only detectable cavity.

(2) *M. C.* did so coincident with the disappearance of a large cavity under pneumothorax collapse, with persistence of cavitation at the contralateral apex.

(3) *L. McK.* did so following marked improvement in extensive noncavity disease in the left lung; cavities in the right lung persisted.

These observations may well have a bearing on the retreatment with streptomycin-PAS of patients from whom streptomycin-resistant tubercle bacilli have been recovered; they may account, in part, for the not unusual but unpredictable *successes* encountered in retreatment, especially when judiciously integrated with collapse.

Summary

A patient with far advanced pulmonary tuberculosis, whose tubercle bacilli were sensitive to streptomycin prior to streptomycin therapy, yielded bacilli with a high degree of streptomycin resistance, and, coincidentally, failed to respond to the drug. After being consistently demonstrated for 20 months, the streptomycin-resistant bacilli disappeared from the sputum coincident with the disappearance of a *left* lung cavity, leaving only streptomycin-sensitive bacilli in the sputum

and a cavity in the *right* lung. The in vivo streptomycin sensitivity of these bacilli was then clearly demonstrated by prompt disappearance of the remaining *right* lung cavity and conversion of sputum during subsequent streptomycin-PAS therapy.

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SARCOIDOSIS WITH MARKED HEPATOSPLENOMEGALY AND JAUNDICE: A CASE REPORT WITH BIOPSY FINDINGS*

By A. E. Dagradi, M.D., N. Sollod, M.D., and J. H. Friedlander, M.D., *Northport, New York*

Since the original description by Boeck [1] in 1899 of the histologic characteristics of the disease sarcoidosis, and the demonstration by Schaumann in 1914

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that it can become generalized, with a particular predilection for the lymphohematopoietic system, an extensive literature has appeared on the subject. This has been reviewed recently in some detail by Freiman.[2]

Hepatic and/or splenic enlargement has been noted to occur clinically in a certain number of cases of Boeck's sarcoid, the incidence of liver enlargement being perhaps slightly less than that of splenic enlargement. The study of postmortem [3, 4] and of biopsy material [5, 6, 7] obtained from patients afflicted with this disease has demonstrated that involvement of the liver and spleen by miliary granulomata is a not uncommon occurrence. However, despite the reported frequency of liver involvement, a significant disturbance of hepatic function has rarely been described. Harrell,[8] in his study of serum protein fractionation tests and of bilirubin tolerance tests in a series of 11 cases of Boeck's sarcoid, concluded that "the liver is damaged to a greater extent than is usually recognized."

The occurrence of jaundice in association with sarcoidosis is reported in only five instances.[9, 10, 11] In four of these cases,[9, 11] there is no proof that the icterus was not the result of other diseases of the liver and biliary tract, since material for pathologic study was not obtained. The fifth case [10] is one that had been subjected to laparotomy, and the icterus was discovered to be the result of common duct obstruction by huge lymph nodes, which disappeared following choledochostomy.

Marked chronic enlargement of the liver and spleen, with the concomitant occurrence of prolonged icterus, has not been described in sarcoidosis, except for an allusion by Longcope: [12] "In other instances the excessive enlargement of the spleen and the liver has led to the diagnosis of Banti's disease." In the case that follows, the positive relationship between the sarcoidosis of the liver and the icterus appears to us to be inescapable, and the bizarre clinical picture which this disease may manifest is emphasized.

Case Report

The patient, a 36 year old colored male veteran, was admitted to the Northport Veterans Administration Hospital on December 14, 1944, with a diagnosis of schizophrenic reaction. His history showed that he had served in the Armed Forces for a short period of time in 1942 but had adjusted poorly and, since his separation from the service in that year had been continuously institutionalized in mental hospitals up to the time of his admission here.

Physical examination recorded at the time of his entry to this hospital was completely negative, and his hospital course was uneventful until January 5, 1948, when he developed an episode of vomiting with a temperature elevation to 101.8° F. It was at this time that the presence of an enlarged liver extending two fingerbreadths below the costal margin was noted. The spleen was not felt. His temperature remained elevated for a period of four days and then subsided to normal limits. On April 3, 1949, fever of 103.6° F. was recorded, and an icteric tinge of the sclerae was present. The abdomen was distended and the liver edge was firm and palpable four fingerbreadths below the right costal margin in the midclavicular line. The spleen was also enlarged and could be felt extending five fingerbreadths below the left costal margin in the midclavicular line. The temperature continued elevated for four days. Studies of liver function at this time revealed a direct van den Bergh of 3.7, indirect van den Bergh of 5.4, a cephalin flocculation test of 3 plus, thymol turbidity of 14 units, and an alkaline phosphatase of 42.7. The total cholesterol was 348, cholesterol esters 53 per cent, total protein 7.39, albumin 3.59 and globulin 3.80.

The red blood cell count was 4,460,000, with a hemoglobin of 13 gm. The white blood cell count was 9,500, with 77 per cent polymorphonuclears. No sickling of the red blood cells was found. No malarial parasites were seen, and red blood cell fragility tests and reticulocyte counts were normal. These laboratory tests were repeated approximately a month later, with little change noted. On June 24, 1949, the temperature rose again to 103° F. and remained elevated for five days. Liver function tests at this time also showed little change other than a slight rise in the direct and indirect van den Bergh reactions. His white blood count showed a leukopenia of 3,650, with 50 polymorphonuclears, 40 lymphocytes, 6 monocytes, 3 eosinophils and 1 basophil. The jaundice continued with varying intensity, and increased amounts

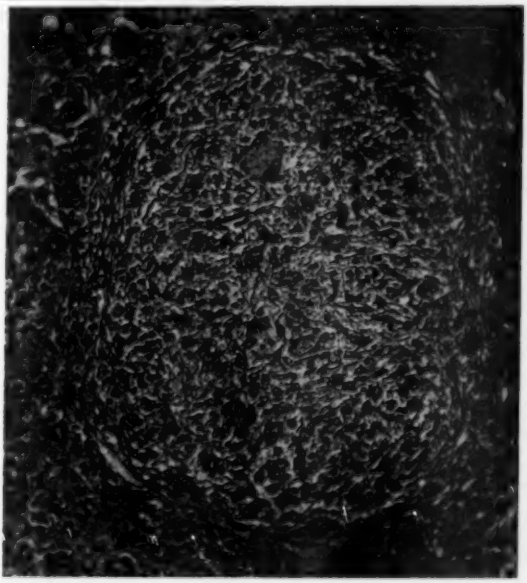

FIG. 1. Section of liver, H. E. stain, low power, showing sarcoid lesion.

of urobilinogen were always found in the urine. The total protein remained elevated, with an A:G ratio of less than 1. Roentgenograms of the chest were normal, as were also those of the hands, feet and nose. Cholecystography failed to show a gallbladder shadow. Gastrointestinal x-ray series showed the descending portion of the duodenum and both the hepatic and splenic flexures of the colon to present marked extrinsic pressure indentations from the greatly enlarged liver and spleen, with displacement of the stomach to the right by the spleen. The Kahn and Wassermann tests were negative, as was also the Congo red test for amyloidosis. Agglutination tests for brucellosis were negative, as were also the spinal fluid findings. The tuberculin reaction was negative in 1:1000 and 1:100 dilutions. The Frei test was negative. Sternal puncture showed relatively normal findings, except for the presence of a slight increase in the proportion of nucleated red cells.

During the months that followed, the patient's appetite continued excellent and there was only a slight weight loss. Itching of the skin was a prominent feature. The liver and spleen gradually increased in size (see figure 3), but at no time was there any lymphadenopathy. Bile was always present in the urine and at times the stools were acholic. The urinary urobilinogen varied from 1 to 40 to 1 to 640. Repeated tests of liver function showed a continued high alkaline phosphatase and a slowly rising cholesterol level, reaching 596 mg. per cent on one occasion. Hyperglobulinemia was a constant finding. Finally a laparotomy was performed on January 10, 1950. This procedure was decided upon instead of a needle biopsy because of the possibility that a remediable surgical condition, such as stone in the

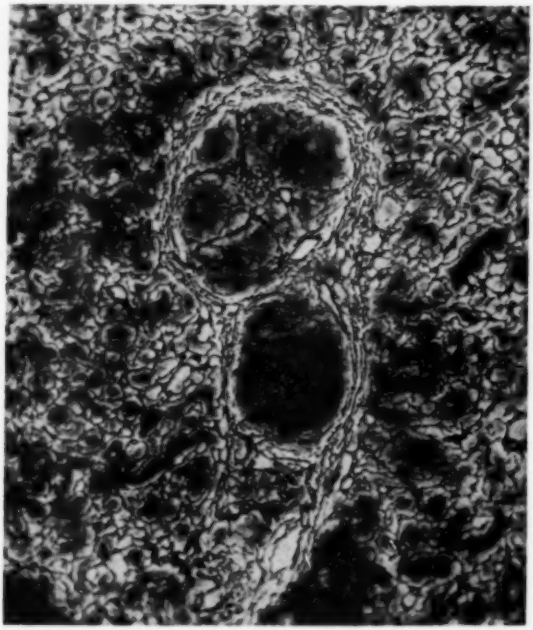

FIG. 2. Sarcoid lesion of liver, showing well preserved reticulum, low power. Silver impregnation.

common duct, might be encountered. The abdomen was opened through a right rectus incision. The liver was found to be markedly enlarged, smooth, firm and normal in color. Numerous pinhead-size grayish nodules were distributed over its surface and lay beneath Glisson's capsule. The spleen was also greatly enlarged and was firm in consistency. Over its surface were scattered tiny grayish opalescent nodules similar to those observed in the liver. The gall-bladder was entirely normal, as were the pancreas and common bile duct. Slightly enlarged, firm, discrete lymph nodes could be felt in the mesentery. The peritoneal surfaces were everywhere smooth and glistening. A biopsy section was removed from the liver and the abdomen closed. The patient's postoperative course was uneventful and he was soon up and about on the ward as usual.

Histological section of the liver biopsy (figure 1) revealed many miliary granulomata scattered throughout and replacing liver substance. Each consisted of epithelioid cells and one or more multinucleated giant cells, and was surrounded by lymphocytes and plasma cells. Surrounding and permeating each granuloma was a fine reticulum. No caseation necrosis was present. These granulomatous lesions distorted the liver cords and compressed the hepatic parenchymal cells. Acid-fast stains were negative. A lymph node from the left inguinal region (figure 2) was removed several days later and examination showed a thin capsule and infiltration of the gland by granulomata identical to those above described. A section of striated muscle showed no abnormality.

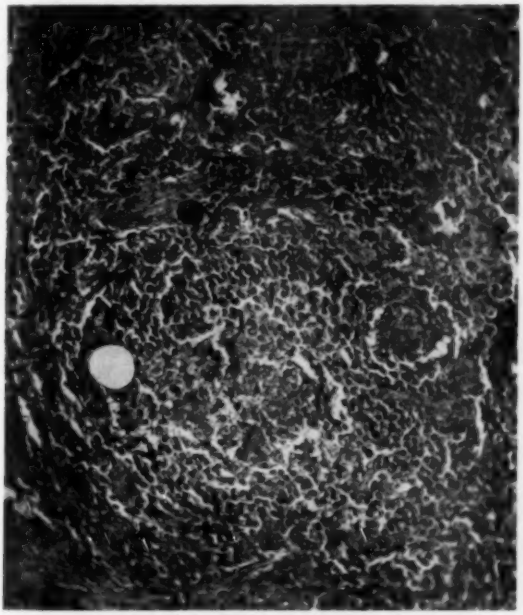

FIG. 3. Section of lymph node, H. and E. stain, low power, showing sarcoid lesion.

DISCUSSION

Because of their characteristic widespread dissemination, chronicity and unequal concentration in the various organs, the lesions of sarcoidosis can produce a variety of clinical syndromes which, from the standpoint of diagnosis, may at times be quite baffling. In order of frequency, these lesions have a predilection for the lymph nodes, lungs, skin and bones, and splenomegaly is not infrequently seen in association with the lymphadenopathy.

The case which we have presented is extremely unusual because of the marked hepatosplenomegaly with associated impairment of liver function and absence of other more characteristic organ involvements which, had they been

present, might have led us sooner to the correct diagnosis. The inguinal node which showed the sarcoid tubercles was removed in order to confirm the findings observed in the liver and spleen. Clinically it was not abnormally enlarged, and we may assume, therefore, that other lymph nodes also contained the lesions.

This case presented a difficult problem in differential diagnosis. Liver function tests showed signs of both obstructive and hepatocellular disease and did not help to clarify the situation. That hepatocellular damage was present was

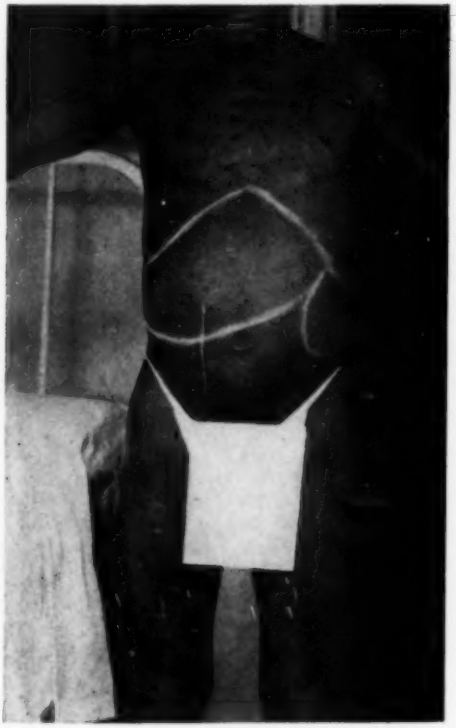

FIG. 4. Photograph of patient, showing the marked hepatosplenomegaly.

evidenced by the strongly positive cephalin flocculation test, the elevated values of the thymol turbidity tests, and the progressive decline in the value of the esterified cholesterol fraction, which dropped from 73 per cent to 30 per cent. The steadily increasing total values for cholesterol, the markedly elevated alkaline phosphatase, the low values for the indirect-reacting bilirubin in comparison to the high values for the direct-reacting type, the presence of bile and urobilinogen in the urine, with, on occasion, the absence of urobilinogen from the stools, suggested an obstructive type of lesion. The relatively unaffected serum albu-

min, an unusual finding in liver disease, confused the issue. This clinical picture seemed to represent a chronic hepatitis or a biliary type of cirrhosis. This case exemplifies the importance of biopsy in ascertaining the correct diagnosis in cases, like this one, characterized by clinical and laboratory findings of a conflicting nature.

Summary

An unusual case of sarcoidosis with marked hepatosplenomegaly and jaundice is presented. The difficulties in diagnosis are stressed and the value of liver biopsy is shown.

Acknowledgment

The authors wish to thank Mr. E. Schmulowitz for the excellence of his technical assistance, and Dr. Harry Zimmerman and Dr. Arthur C. Allen for their assistance in reviewing the microscopic sections.

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ENTEROCOCCAL ENDOCARDITIS: REPORT OF A CASE TREATED WITH AUREOMYCIN *

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We believe the following case is of clinical interest, not only because of the rarity of the occurrence of the infecting organism in endocarditis, but also because of the therapeutic problems involved. Of 921 well authenticated cases of

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bacterial endocarditis chosen at random from the American and British literature, 30 cases,[1-17] or 3.26 per cent, were due to enterococci.

It is of interest to note that Christie,[18] in reporting 269 cases of subacute bacterial endocarditis, failed to incriminate the enterococcus as the etiologic agent in a single case. MacNeal et al.[15] cite the work of Lloyd-Jones, who makes no mention of the enterococcus in listing the microbic findings in 1,000 cases of bacterial endocarditis, though from his own experience MacNeal estimates that about 10 to 15 per cent of patients with bacterial endocarditis are infected with enterococci. Moran [19] found that 20 per cent of the strains of streptococci recovered in cases of bacterial endocarditis were enterococci. The problem of development of resistance to aureomycin in vivo has been minimized by Paine et al.,[20] who induced resistance to the drug in vitro with some difficulty. However, Harvey et al.[11] report two strains of streptococci (one *Streptococcus faecalis*) isolated from blood culture after aureomycin therapy which showed a 16-fold increase in resistance to the antibiotic over the pretreatment sensitivities.

The clinical course of enterococcal endocarditis is not pathognomonic of its etiology; chills, fever, sweats, cardiac murmurs, splenomegaly, petechiae and other embolic phenomena occur. In some respects, however, this disease differs from the endocarditis due to the more common types of alpha hemolytic and nonhemolytic streptococci. Severe precordial pain may occur, examination of the urine may fail to reveal the signs of nephritis so commonly present in subacute bacterial endocarditis, and suppurative lesions are rather common in peripheral organs.[8] There is a great tendency to recur following termination of therapy,[10] and the enterococcus itself is, for the most part, penicillin-resistant.[13]

Of the 30 cases of enterococcal endocarditis cited above,[1-20] 18 are dead. Three [10-11] are probably dead; in two cases [10] death was due to recurrences, and in one case [11] the blood culture was still positive after 107 days of therapy. There were eight cures [5, 11-16] and one probable cure,[16] in which the follow-up had been too short to evaluate the result of therapy. Of the eight cases in which apparent cure followed therapy, two [11, 16] were treated with aureomycin, two [12, 13] with penicillin, two [5, 14] with streptomycin, one [8] with a combination of penicillin and streptomycin and one [15] was successfully treated with bacteriophage. The case in which a probable cure [16] resulted was treated with aureomycin.

The *Streptococcus faecalis* was the etiologic agent in 26 of the above cases of enterococcal endocarditis; in the other four cases,[2, 7] the infecting organisms were not classified beyond the enterococci. The *Streptococcus faecalis* being the type species of the enterococcus group, it is quite possible that no attempt was made to identify the organisms further. The case herein reported was due to the enterococcus, *Streptococcus liquefaciens*, closely related to the *Streptococcus faecalis* species. There was one case of subacute bacterial endocarditis found in the above 921 cases in which the infecting organism was identified as *Streptococcus liquefaciens*.[17]

Case Report

A 34 year old colored male was admitted to the medical ward of the Delaware Hospital on December 21, 1949, with complaints of cough, fever and chest pain. The patient was apparently well until three weeks prior to admission, when he developed a "cold" with rhinorrhea and a dry cough. Two days prior to admission

the cough became more severe and the patient had fever. The following day he experienced vomiting, hemoptysis and substernal chest pain, which was aggravated by cough and deep breathing. Some weight loss was noted during the week prior to admission. The past history revealed only the occurrence of a tender, swollen right ankle several months before admission. This was successfully treated with warm magnesium sulfate soaks.

The physical examination on admission showed a dehydrated, well-developed, well-nourished colored male of stated age lying propped in bed. The respiratory rate was approximately 40 per minute, the pulse rate 128 per minute, the temperature 101.4° F., and the blood pressure 120/50 mm. mercury. No cyanosis was detected. There were several dental cavities. Breath sounds were diminished throughout the chest, and coarse râles were heard in the right lung base posteriorly. The heart beat with a regular rhythm and an increased rate. A systolic murmur was heard at the apex; there was a short, harsh diastolic murmur which was heard best at the second left intercostal space. There were no other findings, and the diagnoses suggested on admission were: (1) lobar pneumonia and (2) rheumatic heart disease with an associated subacute bacterial endocarditis.

Laboratory studies showed a hemoglobin value of 11.2 gm.; 11,600 leukocytes per cu. mm., with 83 per cent segmented neutrophils, 3 per cent nonsegmented neutrophils, 12 per cent lymphocytes and 2 per cent monocytes; a sedimentation rate of 30 mm. in 60 minutes; negative blood serology, and 1 plus albumin with 2 to 5 leukocytes per high power field in the urine. The sputum culture revealed a predominance of penicillin- and aureomycin-sensitive pneumococci and alpha streptococci. The electrocardiogram showed left axis shift and sinus tachycardia. A roentgenogram of the chest revealed cardiac enlargement, some hilar and pulmonary congestion, and no definite consolidation in the lungs.

After two days of penicillin therapy and administration of parenteral fluids there was no improvement in the patient's condition. The temperature fluctuated between 100° and 103° F., the tachycardia and tachypnea persisted, and the patient perspired profusely. The blood culture obtained on admission revealed a growth thought to be pneumococci in a preliminary report. In view of the fact that the patient did not respond to penicillin therapy, and because of the doubt concerning the type of organism isolated from the first blood culture, it was decided advisable on December 23 to administer aureomycin. The dosage was 250 mg. given by mouth every four hours. Oxygen therapy was initiated and Demerol was administered for chest pain.

On December 24 the patient experienced a precipitous drop to normal in temperature and appeared to be much improved, both subjectively and objectively, except for evidence of pulmonary congestion and dyspnea. The temperature remained within normal range for the next two days. On December 27 it was believed that the diagnosis of subacute bacterial endocarditis was substantiated when one area of fresh hemorrhage in the right ocular fundus and three such areas in the left ocular fundus were observed. Tachycardia persisted and the cardiac murmurs noted on admission were unchanged. The organism found on initial blood culture proved to be a penicillin-, streptomycin- and chloromycetin-resistant, aureomycin-sensitive *Streptococcus liquefaciens*. A second blood culture, obtained on December 27, was reported as positive for *Streptococcus liquefaciens* on December 31. On December 28 the patient was digitalized and the penicillin was discontinued.

On January 4, 1950, the aureomycin dosage was increased from 250 mg. every four hours to 1 gm. every four hours. Aluminum hydroxide was administered for five days to allay nausea. Multiple vitamin capsules were given the patient, along with the oral aureomycin. The patient's condition remained poor, dyspnea and tachycardia persisted, and the temperature fluctuated between 99° and 100° F., with

occasional spikes above this level. Rales were continuously present in the lung bases despite supportive therapy.

Five hundred cubic centimeters of type O washed red blood cells suspended in saline were administered to the patient on two occasions and resulted in temporary subjective improvement. On January 7 the oral aureomycin (1 gm. every four hours) was supplemented with 100 mg. of aureomycin intravenously * twice daily. Aqueous penicillin, 600,000 units every three hours intravenously, was begun on January 13. The third blood culture, taken on January 4, showed no aerobic or anaerobic growth after 14 days' incubation. A blood culture on January 10 revealed colonies of *Streptococcus liquefaciens* which were found to be penicillin- and streptomycin-resistant and aureomycin-sensitive.

The patient's condition appeared to deteriorate progressively. On January 18 the intravenous aureomycin dosage was increased to 500 mg. twice daily, in addition to which the patient received 1 gm. of aureomycin orally every four hours, and 600,000 units of aqueous penicillin intravenously every three hours. On January 20 the *Streptococcus liquefaciens* cultures isolated from blood culture number 1 (before therapy) and blood culture number 2 (during therapy) were inhibited in vitro for 24 hours by the following concentrations of antibiotics: penicillin, 13 units/ml.; aureomycin, 1 microgram/ml.; and in 48 hours, penicillin, 13 units/ml.; aureomycin, 2 micrograms/ml. On January 24 the organism was found to be resistant to more than 50 units of neomycin per milliliter in the laboratory, a level considered unobtainable in vivo.

A subsequent roentgenogram of the chest showed generalized cardiac enlargement, pulmonary congestion and pleural effusion at the right lung base. In a second electrocardiogram, taken on January 22, there was evidence of sinus tachycardia and left heart strain.

On January 25 the patient experienced severe cyanosis and dyspnea and died the following day from apparent congestive failure. A venous blood culture obtained on January 19 and an arterial blood culture obtained on January 25 showed no growth after 14 days' incubation.

Autopsy: An autopsy was performed five hours post mortem. The heart weighed 475 gm. The epicardium was smooth and glistening. The myocardium was flabby and faintly orange-red in color in the section made by cutting. There was no evidence of hypertrophy, but there was a slight dilation of the left ventricle without right ventricular dilation. Irregular, firm, yellow, minutely ulcerated vegetations were present on all leaflets of the aortic valve. These vegetations were small, the largest measuring approximately 0.4 cm. in diameter. A slight irregular thickening of the leaflets of the mitral and tricuspid valves was present, but no gross vegetations on these valves could be demonstrated. The pulmonary valve was soft and grossly unchanged. The orifices of the coronary arteries and the arteries themselves were soft and patent.

The right lung weighed 650 gm. and the left lung 500 gm. The surface of each lung was smooth and glistening. All lobes were soft, but there were congestion and edema of both lower lobes. The bronchi and bronchioles of each lung contained large quantities of tan frothy material. A blood culture from the pulmonary artery taken at this time showed no growth after 14 days' incubation.

The liver weighed 1840 gm. Evidence of acute and chronic congestion was present.

The spleen weighed 190 gm. The surface was blue-gray in color and wrinkled, except for an area on the anterior surface which was approximately the size and shape of a hen's egg. In this area the capsule bulged slightly, and the entire area

* Supplied by The Lederle Laboratories, Pearl River, New York.

was white in color. On cut section this area was found to be a septic infarct. A considerable amount of yellow-white pus was readily expressed. No other infarcts were noted in the spleen. A culture from the splenic abscess showed the organism to be a penicillin- and streptomycin-resistant, aureomycin-sensitive *Streptococcus liquefaciens.*

The right kidney weighed 160 gm. Its capsule stripped with ease. At one pole there was a white depressed area measuring approximately 1 cm. in diameter. On sectioning, this area was found to be firm, white, roughly triangular in shape and compatible with a septic infarct. The remainder of the kidney appeared normal. The left kidney weighed 220 gm. The capsule stripped with ease and revealed a smooth red-brown surface. On cut section, two small, firm white infarcts were present in the cortex; each infarct measured 0.4 cm. in diameter. No other gross abnormalities were noted in the remainder of the genitourinary system.

The gastric mucosa revealed a slight petechial congestion. No other abnormalities of the gastrointestinal tract were noted.

Microscopic findings reported on the various tissues substantiated the anatomic findings.

The final anatomic diagnoses were: bacterial endocarditis and myocardial failure; pulmonary congestion and edema; acute and chronic hepatic congestion; septic infarct of the spleen; septic infarct, congestion, and cloudy swelling of the kidneys; slight gastritis.

Bacteriology: The organism isolated from the blood culture of December 27 produced alpha hemolytic colonies on human blood agar plates, these being somewhat larger than those of other streptococci. After 72 hours' incubation, alpha prime hemolysis developed and was accentuated by refrigeration. Growth occurred in broth containing 6.5 per cent sodium chloride and in 0.1 per cent methylene blue milk (with reduction of dye), and on eosin-methylene blue agar plates. Lactose, salicin and mannitol were promptly fermented with the production of acid. Inoculation of Loeffler's serum slant showed liquefaction in 48 hours. Antibiotic sensitivity was determined by the filter disc technic and confirmed with a tube dilution procedure. Subsequent positive isolations from blood culture revealed the same biochemical reactions, and sensitivity or resistance to the antibiotics was unchanged.

Discussion

Much accumulated evidence during the past decade has indicated that serious disease may result from infection with streptococci other than Lancefield group A. This is particularly true of the enterococcus group. Although these streptococci are widely distributed in nature and are normal saprophytes of the human intestinal tract, they may cause disease by extension or conveyance from the intestine to other tissues or organs. The enterococci as a group are not highly virulent, but are more resistant to heating, disinfectants and chemotherapeutic agents than most other streptococci. For these reasons the identification of the group is important as a guide to therapy.

The following characteristics serve to distinguish the enterococci from other streptococci: precipitin reaction with Lancefield group D serum; growth at 10° and 45° C.; resist heating at 60° C. for 30 minutes; growth in media containing 6.5 per cent sodium chloride; growth in 0.1 per cent methylene blue milk. Based on hemolytic activity on blood agar, four groups are recognized: *Streptococcus faecalis* and *Streptococcus liquefaciens* (proteolytic) produce alpha or green hemolysis; *Streptococcus zymogenes* and *Streptococcus durans* produce beta hemolysis. The type of hemolysis and proteolytic action is considered by some

workers to be unrelated to the other significant characteristics. This has resulted in two general classifications of enterococci: the four above-mentioned groups, and a division made up of only *Streptococcus faecalis* and *Streptococcus zymogenes*. This confusion of nomenclature has resulted in the apparent discrepancies cited in the literature.

Finland et al.,[21] in a recent survey of the in vitro sensitivity of various pathogenic streptococci to antibiotics, included 96 enterococcal strains, 14 of which had been isolated from the blood. Although on a weight basis penicillin was the most effective antibiotic for this group, most strains of enterococci required many times the concentration required by other streptococci for growth inhibition. When it is realized that most group A hemolytic streptococci and viridans (alpha) streptococci are sensitive to 0.01 to 0.02 microgram/ml. of penicillin and 1.5 to 2.5 micrograms/ml. of aureomycin, while the enterococci required 1.2 to 12.5 micrograms/ml. and 1.6 to 6.3 micrograms/ml. of penicillin and aureomycin, respectively, it will become readily apparent that the enterococci present a chemotherapeutic challenge.

SUMMARY

1. A case of enterococcal endocarditis due to *Streptococcus liquefaciens* is reported. The strain of enterococcus was sensitive to aureomycin by accepted laboratory tests.

2. The therapy, which included oral and parenteral aureomycin, appeared to sterilize the blood stream but not a splenic abscess.

3. The patient died of congestive failure secondary to valvular and myocardial disease.

4. A brief review of 30 cases of enterococcal endocarditis taken from the literature is presented, along with a summary of the bacteriology of enterococci.

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TRAUMATIC BRAIN-STEM THROMBOSIS: REPORT OF A CASE AND ANALYSIS OF THE MECHANISM OF INJURY*

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Infarction of the medulla oblongata as a sequel to external violence is an uncommon form of vascular accident. Particularly rare are reports of such lesions secondary to manipulation of the head and neck. Two examples of rapidly fatal thrombosis of a vertebral artery or its branches in young adults, in each instance apparently precipitated by chiropractic treatment applied to the neck, have been described by Pratt-Thomas and Berger,[1] who were aware of no comparable cases.

The present report concerns a third instance of this special form of injury during mechanotherapy, from which the patient survived with disabling residua. The mechanism of the neurologic lesion is clarified by reference to experimental studies 23 years ago demonstrating the peculiar vulnerability of the vertebral arteries to occlusion under certain physical stresses.

A standard textbook devoted to traumatic neurologic disease[2] makes no reference to vascular injury of this type, and apart from the report cited above,

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the files of the American Medical Association contain no directly relevant data.* There is, however, a single fragmentary allusion to the laceration of one lateral sinus as the result of injudicious manipulation.[3] In contrast, dislocations or fractures of the cervical spine caused by trauma of this type are relatively common.[4]

Case Report

A 35 year old white single male was admitted to Duke Hospital on April 13, 1950, complaining of a "stroke" which had occurred 19 days prior to admission. He first began to have frequent headache in the left occipital region about five and one-half weeks before admission. The headache migrated later to the right side and at times extended to both frontal areas. It was present irregularly part of each day, without nuchal rigidity, nausea, fever or visual or auditory symptoms. He enlisted the assistance of a chiropractor and for three weeks prior to admission received a series of neck manipulations. The final and sixth adjustment was unusually vigorous, involving stretching and rotary neck movements and then firm pressure on the right side of his neck. At this point, the patient states, he noted sudden dimness of vision, indescribable malaise, diplopia, uncontrollable shaking of the right arm and leg at rest, moderate weakness of the right extremities, numbness of the entire left side of the body, including much of the face, diminished sweating over the right forehead, drooping of the right upper lid, marked dysphagia and hoarseness, and vertigo upon sitting up. The patient was soon afterwards admitted to a local hospital, where he remained for 10 days. During this time, jabbing pains became evident over the right side of his head, and a few days after admission vesicular lesions appeared on the right upper lip, clearing within a week. He also noted frequent and distressing singultus, but no change in taste, hearing or facial motility.

Past History: The past history was marked by three separate illnesses:

(1) At the age of 14 he began to have intermittent joint pains, first noted in his lower back. They improved after chiropractic manipulations, leaving slowly progressive stiffness since then. At the age of 20 he noted the onset of pain low in the cervical spine, and then intermittent pains in the shoulders, hips, ankles and feet. At 22 he was seen in the out-patient clinic at Duke Hospital with these complaints. Roentgenograms showed complete fusion of the sacroiliac joints. A diagnosis of Marie-Strümpell rheumatoid arthritis was made and a brace recommended. During the last five years he had noted intermittent painful swelling and redness of the feet, without fever or localization to either hallux to suggest true podagra. The elbows, fingers, wrists and knees had been spared. Beginning in 1947, he was hospitalized elsewhere on three occasions because of such joint pains, receiving rest, heat, massage and, on one occasion, a course of gold therapy, without striking improvement.

(2) The patient developed a urethral discharge of undetermined nature at 21 and again at 31. On this latter occasion the urethral smear was reported to be negative for gonococci. The complaint was attributed to "prostatitis" and cleared in a short period.

(3) At 16, during a period of severe backache and morning postprandial vomiting, he gradually developed anesthesia and almost complete paralysis of the left arm, which cleared completely after three days. This illness, so suggestive of conversion hysteria, is recalled only vaguely, but he believes that he was under considerable emotional tension at the time because of worry concerning his low back pain.

* Acknowledgment is due to Mr. George E. Hall, of the Bureau of Legal Medicine and Legislation of the American Medical Association, for assistance in the search for published references to chiropractic injury.

Examination: The physical examinations on admission to the neurosurgical service of Duke Hospital and on transfer to the neurologic service eight days later were essentially identical. The patient appeared to be an alert, coöperative and appropriately concerned white man who was emotionally labile and verged upon tears on discussion of his incapacities. His voice was husky and high-pitched. The pulse was 100, with a normal sinus rhythm, and the blood pressure was 150 mm. Hg systolic and 100 mm. diastolic. There was moderate tenderness over the right suboccipital muscles, without bruit or swelling. There was no evident abnormality of any joint except for mild tenderness to palpation over the feet, especially on the right, and slight limitation of motion of the thoracolumbar spine. The neck could be moved freely without pain or stiffness. The general examination was otherwise unremarkable.

Neurologic signs were numerous. The right forehead and cheek were drier than the left. There was mild impairment of hearing by bone-conduction but not air-conduction to a No. 512 tuning fork on the right, and Weber's test was lateralized to the left. There was slight diminution of taste over the right anterior portion of the tongue. There was ptosis of the right upper lid, and the right pupil was miotic. Rotary nystagmus was elicited on left lateral gaze, and there was limited elevation of the palate, and manifest dysphagia. The right extremities were moderately weak, particularly the upper, and presented moderate ataxia and dysdiadochokinesia. There was marked impairment of pain and temperature sensibilities over the area of the right trigeminal nerve, predominantly the first division, but with scattered islands of normal sensation. The corneal reflex was absent on this side. There was moderate impairment of sensibility to pin-prick, temperature and deep pain over the entire left side of the body, including the face. Intense superficial or deep noxious stimulation of the left extremities induced mild aching or tingling. Touch, position and vibration sense, graphesthesia and two-point discrimination were intact. The remainder of the neurologic examination, including superficial and deep reflexes, was unremarkable.

Laboratory Data: The laboratory findings revealed: hemoglobin, 15.5 gm.; hematocrit, 48; and white blood cells, 12,400, with a normal differential. Urinalysis was normal and the blood Kahn was negative. The blood uric acid level on two occasions was 5.7 and 6.5 mg. per 100 c.c. Roentgenograms of the chest and skull, including the foramen magnum, were unremarkable. Spine films showed vertebral bridging and bony proliferation of slight degree in the lower cervical region, and considerably more extensive involvement of the thoracic and lumbar spine. Films of the feet were negative. A right vertebral arteriogram was attempted five days after admission but was unsuccessful. The diodrast solution was observed to spill into neck tissues. Thereafter the patient noticed constant mild aching pain in the right shoulders, brachium and radial side of the forearm.

During his hospital stay the patient showed slowly progressive and spontaneous improvement in coördinated movements in his right extremities. His dysphagia and hoarseness diminished moderately. The ptosis became inconspicuous, but because of difficulty in fusing visual images he tended to keep the right eye closed. His intermittent singultus gradually cleared. The sensory defects, however, failed to change significantly. He received physical therapy and walking exercises, improving daily, so that at the time of discharge he was able to walk with crutches. He was discharged on a regimen of light activity and a low purine diet.

Follow-up: He was seen on a return visit 10 weeks later for further evaluation. At this time he reported gains in strength and coördination for the first six weeks, but little improvement thereafter. He still noted mild difficulty with fusion of objects. His dysphagia and hoarseness had become inconspicuous. The right side of his face still ached and remained numb, he had noted no facial sweating on this

side, and the numbness of the left side of the face was doubtfully less. On four occasions, on abruptly lying horizontally, he had noticed vertigo which was eased by raising the head for a few minutes.

Physical examination at this time revealed the patient to be alert and in good spirits. His voice was still husky and the pulse was 72. Blood pressure was 152 mm. Hg systolic and 100 mm. diastolic. He walked slowly and unsteadily with crutches and very cautiously without crutches. There were a poorly sustained lateral nystagmus on left lateral gaze and a fine irregular sustained rotary nystagmus on right lateral gaze. There were now only minimal dysmetria without dysdiadochokinesia of the right upper extremity alone and no demonstrable weakness. The remainder of the examination was as previously recorded. It was evident that the patient had shown improvement in gait and coördination but little change in sensory and eye findings. The blood uric acid level was now reported to be 8.8 mg. per 100 c.c.

Additional follow-up examinations four and 11 months later revealed no significant changes in his symptoms or signs.

On the basis of these data, it is concluded that the neurologic disease was the result of infarction of the right side of the brain stem, apparently following vigorous neck manipulation. Secondary diagnoses were: rheumatoid (ankylosing) spondylitis of the lower cervical, thoracic and lumbar spine; possible atypical gout in remission but with hyperuricemia, and mild "essential" hypertension.

Discussion

This clinical problem ilustrates clearly some of the instructive anatomic features of lesions in the lateral brain-stem, concerning which many reports have already been published in the past 50 years. A summary discussion of 24 cases has been written by Sheehan and Smyth [5] and need not be reviewed here. Certain issues are raised by the present case which warrant further comment.

The Exact Site and Nature of the Neurologic Lesion: The pattern of symptoms and signs indicates the syndrome of the lateral medullary plate, also termed the retro-olivary syndrome. By the signs and by inference from the symptoms, the principal damage was to structures lying in the right dorso-lateral portion of the medulla: the spinothalamic tract, descending spinal nucleus and tract of the trigeminal, vestibular nucleus, nucleus ambiguus, descending sympathetic pathways in the reticular substance, dorsal spinocerebellar tract, and perhaps also a portion of the cerebellar hemisphere. The quintothalamic tract, crossing over from the left descending spinal trigeminal nucleus, was also involved, although these fibers are usually spared.[5] The spontaneous facial pain on the side of the lesion presumably arose in the damaged ipsilateral spinal trigeminal nucleus and is a relatively uncommon part of the syndrome.[6]

Detailed anatomic studies of this closely packed and vital area of the medulla have shown that, although it has commonly been considered to lie in the domain of the posterior inferior cerebellar artery, it is sometimes supplied by one or more other and smaller branches of the vertebral artery.[7, 8] Variations in the arterial pattern are common. Furthermore, occlusion of the posterior inferior cerebellar artery (Wallenberg's syndrome) cannot always be distinguished with certainty from occlusion of the parent vertebral artery (the syndrome of Babinski-Nageotte), although in the latter circumstance signs of medullary disease are usually even more extensive.[5]

The Mechanism of the Vascular Damage: As indicated above, the clinical picture in this patient does not allow a final inference as to the exact site of the responsible vascular lesion, for in this medullary syndrome either the vertebral artery or one of its branches may be at fault. The experience of Pratt-Thomas and Berger [1] with the two earlier of fatal injury does not settle the issue. Each of these patients was moribund when examined, and the pathologic findings were only approximately similar: in one patient (age 32), recent thrombosis was evident in the basilar, one posterior inferior cerebellar and the opposite anterior inferior cerebellar arteries; in the other patient (age 35), thrombosis had occurred in the basilar, one vertebral and the opposite posterior inferior cerebellar arteries. The failure of the right vertebral artery to fill in our patient during attempts at arteriography allows no definite conclusion that the vessel was thrombosed, for the placement of the needle may have been faulty.

It is evident, however, from consideration of the arterial pattern at the level of the foramen magnum that the vertebral arteries might readily be exposed to injury by strenuous upper neck movement. The vertebral arteries are well shielded and supported as they ascend through the vertebral transverse processes, but are far less protected in their passage from the atlas into the skull. Each vessel follows a sinuous course medially behind the articular process of the atlas to pierce the atlanto-occipital membrane and dura, and then enters the posterior fossa at the lateral margin of the foramen magnum. At this level the vertebral arteries, and also the cord which they flank, must be sufficiently flexible to withstand the stresses of wide arcs of head displacement in anteroposterior and lateral flexion and in rotary movements, in which the atlanto-occipital and atlantoaxial joints play major parts.[9]

The experiments conducted by de Kleyn and Nieuwenhuyse have shown that these anatomic arrangements can somehow compromise blood flow through the vertebral artery in certain head positions.[10] It was noted by these observers that in human cadavers circulation through one vertebral artery was effectively reduced when the head was bent backward (over-extended) and tilted to the opposite side. Since, moreover, anomalies in the size and position of the vertebral arteries are common,[11] it was suggested that individuals with such variations might be particularly susceptible to temporary medullary ischemia during head displacement. These early observations, therefore, together with the more recent pathologic data supplied by Pratt-Thomas and Berger, indicate a likely mechanism for the medullary lesion which may follow vigorous head and neck manipulation. We can speculate that the applied trauma led to damaging compression and subsequent thrombosis of the right vertebral artery or to thrombosis of one of its branches. Such clot formation may have been promoted by stasis, reflex vasospasm, or even fragmentation and release of an intimal plaque at the point of pressure upon the vertebral artery.

The relative infrequency of this general type of vascular accident is a tribute to the resiliency and vitality of arterial walls. It is known that thrombosis may sometimes occur in presumably normal arteries under slight provocation, as in the instance described by Grinker and Guy of anterior spinal artery thrombosis in the midcervical region following stretching exercises.[12] Yet, in general, arterial structures are remarkably resistant to trauma. In the course of experiments by many investigators upon the effects of arm ischemia, the brachial artery

has been repeatedly occluded by a tight but broad cuff for periods of 30 to 40 minutes without apparent arterial damage. Prolonged or repeated pressure upon a narrow segment of an artery, as by a cervical rib upon the subclavian or by a crutch upon the axillary, can induce thrombosis, but even this is rare.[13]

Contributory Factors in the Present Case: Arteriosclerosis, it has long been assumed, will favor intimal injury from compression, perhaps by promoting the local release of thromboplastin, coagulation and platelet deposition.[14] No sign of arteriosclerosis was found in our 35 year old patient. Yet the doubtful evidence for gout (a history of painful feet and the repeatedly elevated blood uric acid levels) prompted further consideration of this possibility, for it has been claimed by some observers that arteriosclerosis is unusually common in gouty patients.[15, 16] This association has been questioned by others and the issue remains unsettled, as does its relevance to the present problem. The arterial hypertension observed in this patient was mild and without demonstrable complication.

The possibility of thrombosis or rupture of a preëxisting aneurysm of the vertebral artery was considered, but was rejected because of the absence of the characteristic history of intermittent symptoms of brain-stem and cerebellar disease and because of the normal cerebrospinal fluid examination.[17] It is of interest that in none of the cases of intracranial vertebral aneurysm recently reviewed were the symptoms clearly aggravated by head or neck stress.[18, 19]

There is no direct evidence that the spondylitis present for so long a time in this patient was a contributing factor to his neurologic illness. It is conceivable that productive changes in and about the diseased intervertebral articulations, or resultant changes in spine mobility, might somehow predispose adjacent tissues to injury during manipulation. Yet in this case, demonstrable arthritis of the spine was evident only in the lower cervical, thoracolumbar and sacroiliac joints. The cervical spine was normally flexible and in its upper portion was unremarkable to roentgen-ray examination.

We are left, therefore, with no reliable proof that this patient's brain-stem injury was facilitated by any preëxisting vascular, metabolic or local joint disease.

The Use of Vertebral Angiography: Examination of the course and size of the vertebral artery by contrast roentgenography has as yet had only restricted use, although the procedure is by no means a new one. Its application to cases of suspected medullary thrombosis will probably remain limited, for the technic, whether by retrograde injection of the subclavian artery or by direct percutaneous injection, is difficult, and in patients with occlusive vascular disease it may carry considerable risk. The prolonged but slowly subsiding pain noted in the shoulder and arm of our patient following the diodrast injection directs attention to one of the complications of this procedure when the blind percutaneous route to the vertebral artery is used. A similar pain, presumably due to injury to the brachial plexus or roots by the needle or the diodrast, was noted also in a patient of the series recently reported by Sugar and co-workers.[20]

Summary and Conclusions

A case is described of the only reported survival from an uncommon and devastating accident—injury to the brain-stem following vigorous chiropractic manipulation of the head and neck. The resulting neurologic syndrome is at-

tributable to infarction of the lateral medullary plate secondary to thrombosis of the ipsilateral vertebral artery or one of its branches. The preëxisting rheumatoid spondylitis and unproved gout in this patient are doubtful predisposing factors.

The brain-stem injury in this patient and in two previously reported fatal cases of similar origin is presumably related to traumatic occlusion of a vertebral artery, for past experimental studies have demonstrated a peculiar vulnerability of this vessel to compression when the head is over-extended and flexed to the opposite side.

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XANTHOMATOUS BILIARY CIRRHOSIS: REPORT OF A CASE *

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WHEN cutaneous xanthomatosis is associated with obstructive jaundice, unless a metastatic process is proved, an exploratory laparotomy seems to be indicated. If there is an enlargement of the liver and spleen with a high blood cholesterol and hyperlipemia, the so-called xanthomatous biliary cirrhosis must be considered.

According to Fuentes [1] and Romano,[2] this condition can be recognized clinically by means of the hypercholesterolemia and ether-extractible bilirubin, and surgery can thus be avoided.

If surgical exploration is carried out, however, and no surgically-removable lesion is found, a biopsy of the liver is in order. One would expect, as Thannhauser and Magendantz [3] did, to find on microscopic examination an obstruction, possibly xanthoma, in the smaller bile passages.

If none is found, one may be dealing with a pathologic condition, for which MacMahon [4] has suggested the term "pericholangiolitic biliary cirrhosis," the pathogenesis of which is still not clear. The following case closely resembles those that he describes and those that have been reported as xanthomatous biliary cirrhosis.

CASE REPORT

Six years and four months before her death on December 14, 1949, this 36 year old white married woman began to have jaundice, light stools and dark urine. A month later, a few small yellowish nodules appeared on her chin. Similar lesions accompanied by itching then developed on her hands and arms. Her first admission to the Greenwich Hospital for this illness was on January 20, 1944, five months after the onset of jaundice.

During the preceding year, following the birth of her only child, she had lost 20 pounds in weight.

The family history was noncontributory.

The past history included a chronic appendicitis, and myoma and retroversion of the uterus, for which an appendectomy, myomectomy and uterine suspension had been done two years before the onset of jaundice.

Physical examination revealed a well nourished and well developed young adult white female with markedly icteric skin and sclerae but in no acute distress. The presence of xanthelasma was noted. The hands and chin were covered with soft yellowish raised lesions ranging in size from that of a millet seed to .5 cm. in diameter. The heart and lungs were normal. The liver was enlarged to three fingerbreadths below the costal margin and was smooth, firm and nontender. The spleen was only slightly enlarged.

Laboratory findings included a blood cholesterol of 330 mg. per cent, an icterus index of 100, an erythrocyte sedimentation rate of 25 mm. per 60 minutes, a red blood cell count of 3,830,000 and a white blood count of 4,550, with a normal differential. Three weeks later a 17 per cent eosinophilia was reported. The urine revealed a faint trace of albumin, and the stools contained a small amount of bile. The galactose tolerance test was normal. The Kahn was negative.

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A skin biopsy (figures 1 and 2) taken from the left forearm on January 24, 1944, revealed xanthoma. The pathologist associated the skin lesion, the elevated cholesterol and the jaundice with a "manifestation of deranged fatty ester metabolism probably due to liver or gall-bladder disease."

The patient received sulfaguanidine, milk of magnesia, glucose infusions, and one transfusion of whole blood, and was given a high protein, high carbohydrate, low fat diet. She was discharged improved on the twenty-seventh day of hospitalization. A diagnosis of cholangitis was recorded.

A month later, on March 10, she was admitted to the Presbyterian Hospital in New York City, with an increase in the jaundice and a spread of the skin lesions.

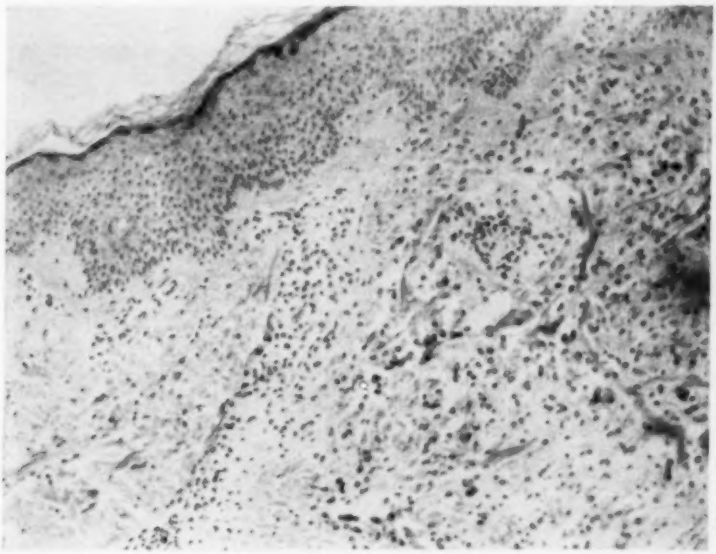

FIG. 1. Skin biopsy, January 24, 1944, showing a xanthoma.

Xanthomatous nodules were noted on the eyelids, ears, chin, palms, axillae and antecubital fossae. She had icteric skin and sclerae. The liver was found to be enlarged to the level of the iliac crest, and the spleen was felt two fingerbreadths below the costal margin.

Laboratory studies showed a cholesterol of 916 mg. per cent, which rose to 1,150 mg., then fell to 700 on the same admission. There was 1 to 3 plus bile in the urine, but no urobilinogen. A prothrombin time of 41.5 seconds was reduced on vitamin K therapy to 20.9 seconds. Serum alkaline phosphatase was 17.6 Bodansky units and later rose to 36.1. Serum protein was normal. Bilirubin was 4.5 mg. per cent. Total blood lipids were 1,830 mg. per cent. The cephalin flocculation was 1 plus. Duodenal drainage showed no B bile, no cholesterol crystals, no pigment granules. Intravenous hippuric acid test was normal.

Surgical exploration on March 29 revealed an enlarged liver with many red patches but no apparent scarring. The gall-bladder was thin-walled and contracted,

and contained very little bile and no stones. The common duct was explored and irrigated by means of a T-tube. Hepatic bile from the T-tube showed normal cholesterol and solid matter concentrations.

Histologic examination of a punch biopsy of the liver (figure 3) disclosed a well preserved lobular architecture with dilated intralobular capillaries. There were numerous plugs of bile pigment in the bile canaliculi. Groups of liver cells showed cloudy swelling and granular degeneration, with an increase of fibrous tissue and numerous mononuclear inflammatory cells in the portal spaces. No xanthoma cells were seen.

The pathologist reported an obstructive jaundice with ascending cholangitis. The biopsy suggested that the peripheral deposits of lipoid and increase in cholesterol were secondary to the obstruction.

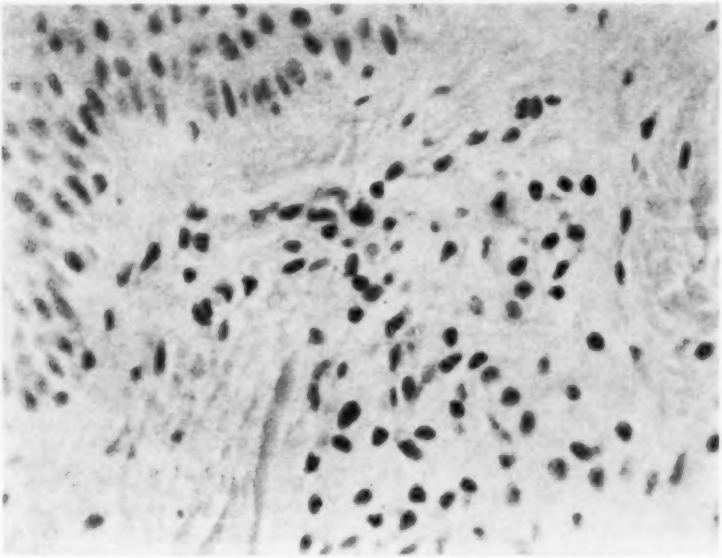

FIG. 2. Skin biopsy (higher power), showing xanthoma cells with small nuclei and foamy cytoplasm.

It was felt that the patient's hepatic difficulty lay in the excretory phases of her cholesterol metabolism, with blockage apparently between the hepatic sinusoids and the larger intrahepatic bile ducts. The liver appeared able to excrete hippuric acid and bilirubin but not cholesterol or phosphatase.

The patient's postoperative course was good, and she was discharged on the thirty-sixth hospital day.

During the course of the year following discharge there was continued improvement, with gradual disappearance of the jaundice and all the xanthomatous lesions but those of the eyelids. Annual cholesterol determinations were said to show improvement. A low cholesterol diet was followed for one year only.

She remained in fair health until October, 1948, 14 months before her death, when she began to have intermittent episodes of diarrhea, with 10 bowel movements

daily. About six months before her death she noticed swelling of the legs, followed a few days later by swelling of the abdomen. At about this time her menses ceased and polydipsia and polyuria were noted for a few days.

Treatment with diuretics and liver extract failed to bring about improvement, and she was re-admitted to the Greenwich Hospital on July 10, 1949.

Physical examination again revealed icteric skin and sclerae, with bilateral palpebral xanthomata, hepatosplenomegaly and evidence of ascites.

Laboratory findings were as follows: hemoglobin, 7.5 gm.; red cell count, 3,280,000; white count, 3,150, with a normal differential; icterus index, 35; total cholesterol, 172 mg. per cent, of which 88 mg. were free cholesterol and 84 mg. cholesterol esters. Total protein was 6.7 gm. per cent; albumin, 4.9 gm., and globulin,

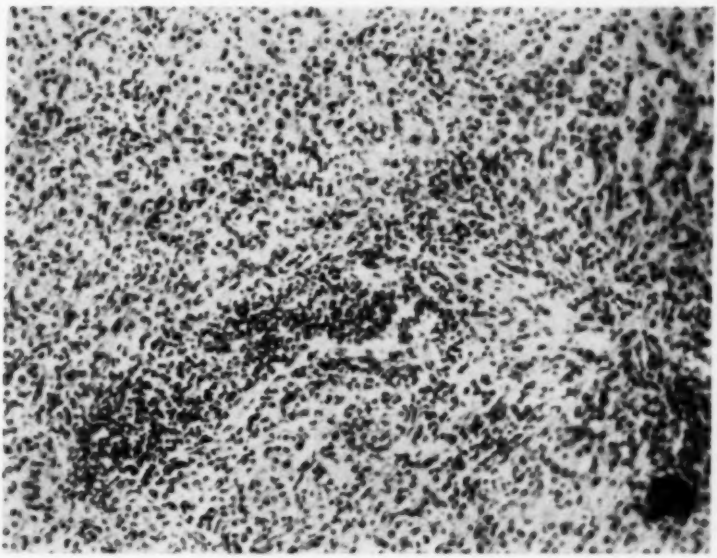

FIG. 3. Liver biopsy, March 29, 1944, showing dilated intralobular capillaries, marked round cell infiltration and a bile-filled canaliculus. No xanthoma cells.

1.8 gm. Cephalin-cholesterol flocculation was 3 plus (48 hours). Prothrombin time was 33 seconds (control, 15 seconds). The stools were brown and contained bile. Bile was found in the urine.

The sternal marrow was normal. Roentgenograms of the skull revealed normal findings.

On intraheptol, methionine, choline, glucose infusions, and a high carbohydrate, high protein, low fat, low cholesterol diet, there was some general improvement and the patient was discharged on the thirty-first hospital day.

The same treatment, together with as much yeast as she could tolerate, i.e., 20 gm. daily, was continued at home. The patient recovered some strength and a moderate sense of well being.

However, portal obstruction increased and the re-accumulation of ascites be-

came more rapid, so that during the last few months an abdominal paracentesis had to be performed about once a week and sometimes more often.

During this time she developed a number of spider hemangiomata, most numerous in the upper anterior chest and neck, and a brownish discoloration of the skin with a vitiliginous area over the forehead.

The serum albumin fell progressively until at the end it was 2.1 gm. per cent, while the globulin rose to 3.1 gm. A condition of anasarca, which was present terminally in varying degree, was attributed largely to the hypoalbuminemia. The cholesterol dropped to 137 mg. per cent, while the alkaline phosphatase remained slightly elevated, the final determination being 4.8 S.J.R. units.

The anemia became more marked despite the transfusions.

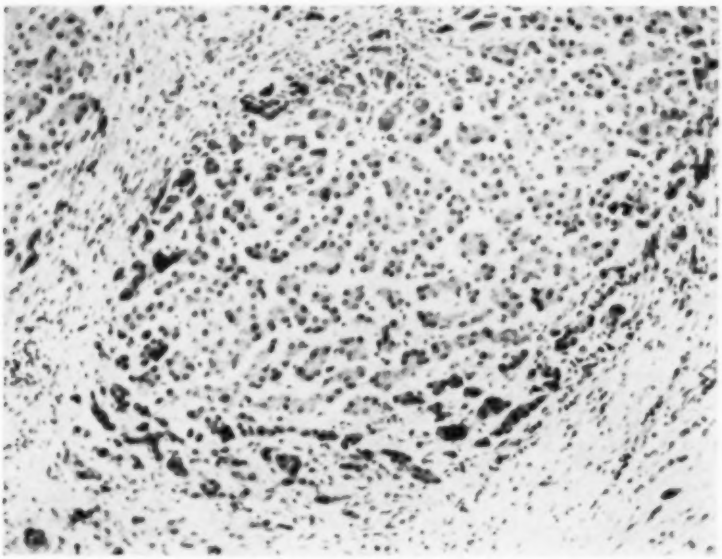

FIG. 4. Liver autopsy, December 14, 1949, showing a distorted lobule with clumps of bile in the canaliculi. No xanthoma cells.

During the last six weeks, gastrointestinal hemorrhages recurred with increasing frequency and severity, requiring repeated blood transfusions and re-admissions to the hospital. A pleural friction rub developed on the left, and there was evidence of pleural thickening and effusion.

Her condition became progressively worse, and she finally lapsed into coma and died on December 14, 1949, six years and four months after the onset of her disease.

Autopsy Findings: The important findings at autopsy were as follows: an enlarged liver, weighing 2,100 gm., an enlarged spleen, weighing 1,030 gm., and abdominal lymphadenopathy.

Other pathologic features included esophageal varices, with hemorrhage, dilated submucosal veins throughout the gastrointestinal tract, bilateral bronchopneumonia, and fibrinopurulent pleuritis on the left.

The liver had a thickened capsule and an intensely green parenchyma which was studded with greenish yellow nodules varying in size from 2 to 3 mm. in diameter. The larger bile ducts appeared to be normal.

The gall-bladder was shrunken and small. It was surrounded on three sides by liver, and contained a grayish pink mucopurulent material.

On microscopic examination of the liver (figure 4), the irregular nodules of varying size, most of them without a central vein, were again seen. There were dilated sinusoids and, in some areas, clumps of bile in the canaliculi. At the periphery of the lobules the liver cells were swollen with bile pigment, and active degeneration was taking place in many of them. Encircling the liver lobules were broad bands of fibrous tissue with a varying degree of lymphocytic infiltration. Bile duct proliferation was not noted.

The spleen contained several hemorrhagic infarcts. The increase in size was due to overgrowth of the framework and the red pulp.

Enlargement of the abdominal lymph nodes was due to hyperplasia of the reticuloendothelial cells in which the cytoplasm was filled with bile pigment.

Special stains of all the major organs failed to reveal the presence of iron.

Comment

There are certain features of this case, and of the few similar ones reported as xanthomatous biliary cirrhosis, that suggest its relationship to a number of metabolic and endocrine disturbances. But the sequence of pathologic events is not clear.

If one calls it a disorder of fat metabolism, which it may well be, the primary organ affected is still not established. In any disease of metabolism one would suspect liver involvement, and since jaundice usually precedes the development of cutaneous xanthoma it is not illogical to assign the primary rôle to this organ. On the other hand, of 55 cases of cutaneous xanthoma reported by Montgomery,[5] only eight had associated hepatic disease.

Involvement of the reticuloendothelial system is suggested by the first case reported by Burger and Grutz. This was an 11 year old boy who had cutaneous xanthomatosis, high blood cholesterol and hyperlipemia, with hepatosplenomegaly but no jaundice. The reticuloendothelial system was outlined by deposits of lipoids, and there were large cells resembling those seen in Niemann-Pick disease.

There are a number of traits in common with Gaucher's disease, but jaundice and ascites are rare in this condition, which usually begins insidiously in infancy or childhood.

Likewise, there is a resemblance to Hand-Schüller-Christian disease, in which there is a hepatosplenomegaly in association with hypercholesterolemia; but there were no bony changes in the skull or exophthalmos, and diabetes insipidus, if present, was in mild form.

A pancreatic factor is suggested by the close resemblance of xanthoma diabeticorum in the early stage to xanthoma tuberosum. Romano [2] even describes a case of diabetes mellitus associated with xanthomatous cirrhosis. This author considers xanthomatosis a systemic metaplastic disease of the reticuloendothelial system, often of hereditary or familial character.

The hereditary nature of xanthoma is stressed by Alvoord,[6] who made a study of 30 affected persons in a family. All had a lipemia which was inherited

as a simple autosomal dominant trait. More than half had a history suggesting disease of the coronary arteries.

Thannhauser and Magendantz [3] have stated that the cirrhosis is an expression of a systemic disease, primary xanthomatosis, and that the essential change is the xanthomatous cell which in the liver causes narrowing of the bile ducts.

Although the true nature of xanthomatous biliary cirrhosis remains obscure, its resemblance to a wide variety of diseases suggests that all of them may be related etiologically and, in fact, may be different expressions of the same pathologic process. Further study may reveal a common denominator, throw more light on the metabolism of cholesterol, and yield a clue to the cause of a very common disease, namely, atherosclerosis.

A high cholesterol has long been associated with coronary atherosclerosis. In fact, this condition has been produced experimentally in rabbits by feeding them a high cholesterol diet.

Since the cause of xanthomatous biliary cirrhosis is unknown, the treatment is understandably disappointing. Lipotropic substances such as choline and methionine, and dietary measures, notably low fat and low cholesterol, and vitamins, especially vitamins K and B, may be of value.

Lipotropic substances and external biliary drainage, used by Pollard, Eckstein and Ransom [7] in a case similar to the one contained in this report, produced no outstanding effect in a 16 month period of observation.

Lipocaic, the pancreatic hormone, has been shown by Huber, Brown and Casey [8] to prevent atherosclerosis in rabbits fed a high cholesterol diet. This hormone is also described by Dragstedt.[9] When administered to depancreatized dogs maintained on insulin, it restores the content of blood lipoids to normal and mobilizes the fat from the liver.

However, its use in a case of xanthomatous biliary cirrhosis reported by Comfort, Shepard and Snell [10] did not affect the values for blood lipoids.

Summary

A case of xanthomatous biliary cirrhosis is reported. Skin and liver biopsies were taken in the early stage of the disease, six years before the patient's death. She was closely observed throughout her course, and an autopsy was performed.

While the combination of xanthoma with this form of cirrhosis is rare, several features in common with a number of metabolic, endocrine and reticuloendothelial diseases, suggest that many of these diseases may be related.

Acknowledgment

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ORTHOSTATIC HYPOTENSION: REPORT OF A CASE REFRACTORY TO VASOCONSTRICTOR DRUGS; WITH OBSERVATIONS ON USE OF DESOXYCORTICOSTERONE, L-NOREPINEPHRINE, ACTH AND VASOPRESSOR POTENTIATING SUBSTANCES *

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IN 1925, Bradbury and Eggleston [1] reported a syndrome, previously undescribed in medical literature, characterized by a fall in blood pressure in the erect position or on exertion, slow, unchanging pulse, decreased sweating, diminished basal metabolic rate, intolerance to heat, increased reactivity to epinephrine, decreased reactivity to atropine, blood urea nitrogen at the upper limits of normal, and unchanging electrocardiogram during blood pressure drop.

The exact etiology of orthostatic hypotension has remained obscure, despite 40 or more case reports in the medical literature. The consensus favors a lesion in the central nervous system, probably located in the hypothalamus, which results in a diminution or loss of sympathetic outflow impulses from the cardioaccelerator, vasoconstrictor and diaphoretic centers.[2, 3]

The patient to be described is a classic example of orthostatic hypotension without compensatory tachycardia. There was no evidence of a demonstrable

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lesion in the hypothalamus to explain the symptoms, other than the loss of sympathetic nervous function.

During hospitalization it was thus possible to study the effects of vasopressor substances, desoxycorticosterone, adrenocorticotropic pituitary hormone, *l*-norepinephrine and vasopressor potentiating substances on a subject devoid of normal vasomotor control. The results of these observations are presented below.

Case Report

A 52 year old white male of Italian birth was admitted to Wadsworth General Hospital on January 28, 1949, from the Los Angeles Veterans Administration Domiciliary with complaints of recurrent attacks of syncope in the erect position, weakness, inability to sweat, and easy fatigability since 1945.

Present Illness: In one week of March, 1944, he gave two one-pint blood transfusions. In April, 1945, the patient developed progressive fatigue on exertion, weakness and dizziness. In June, 1945, he had several episodes of fainting while standing. A private physician in Brooklyn, New York, treated the patient for probable coronary thrombosis and kept him in bed for five weeks, although an electrocardiogram was described as showing no evidence of myocardial infarction. He was unable to continue working as a clothing presser in a garment factory following his hospitalization. In 1946, seeking improvement in a warmer climate, the patient drove to California, without mishap. Because of a recurrence of syncope in the erect position, he was hospitalized at the U. S. Naval Hospital, Corona, California, December 12, 1946, where he was found to have marked orthostatic hypotension. Records from the latter institution revealed that ephedrine, in doses of three-eighths of a grain five times daily, was ineffective in maintaining his blood pressure. Although Addison's disease was excluded as an etiologic factor, the patient was given desoxycorticosterone acetate, 5 mg., three times weekly, and extra sodium chloride. After several weeks, the patient developed hypertension in the supine position, averaging 162 mm. Hg systolic and 100 mm. diastolic, and was able to stand for several hours maintaining a blood pressure of 60/40. He was discharged as improved June 7, 1947, on maintenance of desoxycorticosterone acetate and sodium chloride.

He was admitted to the Los Angeles Veterans Administration Center Domiciliary on June 10, 1947. The admitting medical officer was unable to obtain a blood pressure in the upright position, and the patient admitted that he had not been using his medication. Essential laboratory data found to be within normal limits included an electrocardiogram, serologic test for syphilis, chest roentgenogram, fasting blood sugar and blood cholesterol. The urine showed 1 plus albumin, with three to five granular casts per high power field; blood sodium chloride was 412 mg. per cent; non-protein nitrogen was 18 mg. per cent; basal metabolic rate was minus 20.

He was treated with desoxycorticosterone acetate,* 10 mg. twice a week, and sodium chloride, 1.0 gm. three times a day. By July, 1947, his standing blood pressure was maintained for short intervals at 98/90, and blood sodium chloride had risen to 528 mg. per cent. The patient was able to tolerate several convalescent furloughs at home, although he had occasional fainting spells when he stood for any great length of time. An electroencephalogram on October 12, 1948, revealed moderate diffuse cortical abnormality consistent with epilepsy. He was given dilantin sodium, gr. 1.5 twice daily, without benefit in preventing episodes of syncope in the erect position. In December, 1948, on numerous occasions the patient became faint while sitting in his wheel chair. He was sent to Wadsworth General Hospital for observation.

* A commercial preparation of 11-desoxycorticosterone acetate in sesame oil, containing 5 mg. per c.c., was employed.

Past History: The past history was essentially negative except for pneumonia in 1917. The patient was childless, although married for many years. His mother had died of hypertension.

Physical Examination: The patient was a mild mannered, well developed and nourished gray-haired middle-aged white male, who appeared lethargic, but was cooperative and oriented. Physical examination on admission was negative except for grade I retinal arteriosclerotic changes, hyporeflexia, and dry smooth skin. The blood pressure was: supine, 166/110; sitting, 122/86; standing, 0/0. While standing the patient exhibited muscular twitching and slumped to the floor. His pulse remained constant at 72.

Laboratory Studies on Admission: The red cell count was 3,900,000; hemoglobin, 78 per cent; sedimentation rate, 16 mm. The white cell count was 10,000; differential count showed 72 per cent neutrophils, 21 lymphocytes, one monocyte, and six eosinophils. The blood urea nitrogen was 19 mg. per cent and 22 mg. per cent. Fasting blood sugar was 75 mg. per cent. Basal metabolic rate was minus 16 and minus 18. Cardiolipin serologic test for syphilis was negative. The serum sodium was 357 and 387 mg. per cent. Serum chloride (as sodium chloride) was 554 and 568 mg. per cent. Urinary 24 hour 17-ketosteroid excretion was 8.5 mg. Protein bound serum iodine was 5.0 and 5.2 micrograms per cent. Urinalysis showed occasional white blood cells and hyaline casts. Serum cholesterol was 231 mg. per cent, with cholesterol esters 187 mg. per cent. Total serum protein was 7.41 mg. per cent. Albumin-globulin ratio was 1.4. The chest roentgenogram, flat roentgen-ray film of the abdomen, and skull roentgen-ray series were within normal limits. Electrocardiographic studies with unipolar leads revealed evidence of myocardial changes.

Lumbar puncture revealed a pressure of 90 mm. of water, clear fluid; the Wassermann test, colloidal gold, protein, globulin and cell count were within normal limits.

Electroencephalogram showed diffuse cortical changes consistent with cerebral anoxemia secondary to orthostatic hypotension.

The Kepler-Power water deprivation test was negative.

Oral one dose, three hour glucose tolerance test was within normal limits.

Further Clinical Study: Tilt table test on February 8, 1949:

	BP	P	VP	EKG	Eyegrounds	Sensorium
Supine	110/80	80	3 cm.	Neg.	Veins congested	Clear
Head down 30°	160/110	80	3 cm.	Neg.	Veins dilated and congested	Clear
Head up 30°	80/60	80	4 cm.	Neg.	Veins full	Clear
Head up 45°	65/55	Weak, thready 82	Unable to obtain	Neg.	Veins thin, fundus pale	Lethargic, dizzy
Head up 80°	0/0	Unable to obtain	Unable to obtain	Gross muscle twitchings	Arterioles and venules thin and pale	Gross muscular twitchings; syncope

Pressure on each carotid sinus did not alter heart rate or blood pressure or electrocardiogram in supine or sitting position.

In order to test sensitivity to epinephrine, 0.01 mg. was injected intravenously while the patient was supine. The blood pressure rose from a control of 98/60 to 240/130 in one minute and remained elevated, returning to the previous level in 20 minutes. The pulse also rose to over 160, paralleling the blood pressure in returning to resting level.

Atropine (gr. 1/150) was injected subcutaneously with no appreciable change in blood pressure or pulse during a period of 30 minutes.

The patient was hyperventilated for three minutes in the supine position, with no significant change in blood pressure, pulse or sensorium.

A cold pressor test revealed a slight rise in blood pressure with an unchanging pulse in the supine position.

Clinical Course with Result of Treatment: Bandaging of the lower extremities with elastic bandages alone and in combination with a tight abdominal binder (Kerr-Langen belt) did not prevent a marked fall in blood pressure and syncope in the erect position.

The patient was given 10 mg. of Paredrine * intravenously and the blood pressure rose from 130/95 to 220/150 within 30 seconds in the supine position; however, on standing, the blood pressure fell to an imperceptible level. Paredrine, 200 mg., was given orally on three occasions, following which the blood pressure rose rapidly to high levels and the patient was able to stand for periods up to one hour. However, the response varied each time and this medication was not considered to be of value in maintaining the patient over a prolonged period. Following each oral administration of Paredrine, urine was saved for three hour periods and analyzed for traces of the drug. It was found that the concentration in the urine was markedly reduced in this patient as compared to normal excretion following oral administration. Consequently, it was assumed that Paredrine was metabolized in an abnormal manner in this patient.

Neosynephrine † (10 mg.) was injected intramuscularly and a marked rise in blood pressure occurred similar to the rise produced by epinephrine and Paredrine when they were given intravenously. Neosynephrine was then given orally in single doses up to 110 mg. every morning. There was a variable response to therapy, and the patient was still unable to tolerate the erect position.

MacLean's head-up position,[4] using 18 inch blocks under the head of the patient's bed, was instituted for a three week period without elevation of the blood pressure level.

Because of previous success with desoxycorticosterone acetate in oil (DCA), as reported in the literature, in treating orthostatic hypotension,[23, 24, 25, 26] and because of its effect in elevating the blood pressure in this patient previously, it was decided to reinstitute this therapy as follows: Before treatment, blood volume studies in the supine position with Evans blue dye yielded a blood volume of 6,600 c.c. (calculated blood volume was 6,650 c.c.).‡

The patient was given 12 gm. of sodium chloride daily for two weeks without an increase in blood pressure. Blood volume studies were repeated in the supine position while the patient was on sodium chloride therapy, and the blood volume was 7,000 c.c.

On May 17, 1949, treatment with desoxycorticosterone acetate in oil was begun. The patient received 5 mg. of the drug intramuscularly up to three times daily. After one week of treatment the patient felt less fatigued. He developed a hypertension up to 224/142 in the supine position. He was able to maintain his blood pressure for several minutes in the erect position and for several hours in the sitting position. An electrocardiogram on June 19 was abnormal, showing S-T segment depression and inversion of T waves in Leads I, II, aV_L, V_3, V_4, V_5 and V_6, and was interpreted as indicative of marked myocardial changes consistent with hypopotassemia. The serum potassium at this time was 14 mg. per cent and serum sodium

* Paredrine hydrobromide, Smith, Kline, and French Laboratories, Philadelphia.

† Neosynephrine, Winthrop-Stearns, Inc., New York, N. Y.

‡ Blood volume studies performed by Abraham Schneiderman, M.D., former medical resident at Wadsworth General Hospital.

was 309 mg. per cent. Desoxycorticosterone acetate was discontinued and oral potassium was administered, and the electrocardiogram on July 12 revealed a return of S-T segments in Leads I, aV_L, V_3, V_4 and V_5 to the baseline.

In July the patient was maintained on 5 mg. desoxycorticosterone acetate and 9 gm. of sodium chloride daily. On this regimen he was able to sit for long periods without becoming faint, but was unable to stand for more than several minutes without fainting. There was no evidence of myocardial insufficiency.

A U. S. Navy antiblackout ("G") suit was then obtained and all medication was discontinued. Upon adequate inflation of the suit there was no change in blood pressure, and the patient developed hypotension and syncope when he attempted to stand. This differs from the findings of Stead and Ebert,[23] who observed that the application of external hydrostatic pressure (by standing their patients in water up to the level of the heart) prevented a fall in blood pressure.

Since Selye,[20] Symington and Goodall [21] and others have reported vascular lesions following the prolonged use of desoxycorticosterone and related steroids, we attempted to find a pressor substance which might be equally effective and yet not produce severe vascular changes. Goldenberg et al.[15, 16] have demonstrated that *l*-norepinephrine is an effective substance in maintaining arterial pressure in the acute hypotension associated with thoracolumbar sympathectomy. Accordingly, it was felt that *l*-norepinephrine might be of value in supporting the blood pressure in this patient. He was given .01 mg. *l*-norepinephrine * intravenously in the supine position and his blood pressure rose to 270/130 for several minutes; hypotension returned when the erect position was assumed. On several occasions the patient was infused with an aqueous solution of *l*-norepinephrine intravenously. However, on a relatively constant infusion level of .02 to .03 mg. per minute, given over a 30 minute period while the patient was standing, the blood pressure dropped from 150/110 to an unobtainable level. Because of the variable response obtained, it was thought that no further advantage would be realized with a preparation of *l*-norepinephrine in oil as opposed to an intravenous aqueous infusion.

The possibility that the patient's hypotensive reflexes were hyperactive was suggested, and the use of intravenous procaine was recommended [18] in an attempt to alter reflex pathways. Five hundred milligrams of procaine were given intravenously on several occasions, without any change either subjectively or on the blood pressure.

It has been shown that the antihistamine compounds enhance the pressor response to epinephrine. The mode of action is not clearly understood. Yonkman et al.[28] have postulated that pyribenzamine might inhibit amine oxidase or tyrosinase. Haley and Harris [19] have shown that the antihistaminic drugs, not related to acetylcholine, have a vasoconstrictor action on the precapillary sphincters of the mammalian capillary bed. Chen and Russell [27] have suggested the blocking of vasodepressor receptors as a possible mode of action of the antihistaminic compounds. Sherrod et al.[31] believe that the antihistamine drugs diminish or block vagal cardioinhibitory impulses.

Our patient was given varying doses of Benadryl † intravenously. Seventy-five milligrams of this drug intravenously raised the blood pressure from 110/80 in the supine position to 150/110. This pressure was maintained for about 40 minutes but dropped immediately when the patient attempted to stand. Benadryl was then given intravenously in combination with *l*-norepinephrine and Paredrine, but no potentiating effect on these pressor substances was noted.

Secker [29, 30] has demonstrated that the adrenal cortex is involved in the formation of adrenergic transmitter. Meier and Bein [22] claim that the adrenals discharge into the blood stream one or more substances essential for the pressor action of epi-

* The *l*-norepinephrine was supplied by Dr. M. L. Tainter, of the Sterling Winthrop Research Institute.

† Diphenhydramine HCl, Parke, Davis & Co., Detroit, Michigan.

nephrine. Because of the above work, this patient was treated with adrenocorticotropic hormone * for a two day period. The initial dose of 50 mg. of ACTH produced a normal eosinophil response. Subsequently, ACTH was given in a dosage of 20 mg. every six hours for a 36 hour period, without a change in reflex vasomotor response. At the height of ACTH activity an infusion of *l*-norepinephrine was given but no synergistic response was demonstrated.

It was decided to discharge the patient on a maintenance dose of desoxycorticosterone acetate; accordingly, he was placed on 5 mg. of the drug daily. While on this dosage, he began to retain fluid, manifested by a weight gain of 12 pounds in one week. Desoxycorticosterone was reduced to 2.5 mg. daily. The patient was also given supplementary potassium. He has been seen at intervals during the past eight months, and is able to be up in a wheel chair for long periods of time without untoward effects.

Conclusion

A patient with marked orthostatic hypotension without tachycardia was observed over a period of three years. It was not possible to maintain the blood pressure within a physiologic range in the erect position with sympathomimetic vasoconstrictor drugs (Paredrine,[5, 10] epinephrine,[3, 6, 8, 9] neosynephrine [6]), mechanical devices [6] (abdominal binder, leg bandages, and a U. S. Navy antigravity suit), or by posture (MacLean's head-up position).[4]

l-norepinephrine was given by constant intravenous infusion without maintaining the blood pressure above the syncope level in the erect position. Intravenous procaine did not inhibit vasodepressor (hypotensive) reflexes. A vasopressor potentiating substance (intravenous Benadryl) was administered, with a transient moderate rise of blood pressure in the erect position. When administered simultaneously intravenously with Paredrine or *l*-norepinephrine, Benadryl had no synergistic effect.

Pituitary adrenocorticotropic hormone was administered intramuscularly in order to supply adrenal cortical epinephrine-potentiating factors (adrenergic transmitter). There was no response on short range therapy (three days) alone, or in combination with *l*-norepinephrine.

Desoxycorticosterone acetate in oil was administered intramuscularly at various times in a three year period to elevate and maintain the blood pressure above the syncope level in the sitting and standing position. However, some of the other effects of prolonged administration of desoxycorticosterone acetate became manifest.[11, 12, 13, 14, 20, 21, 22] These consisted of a diastolic hypertension over 110 mm. in the supine position, electrocardiographic evidence of myocardial changes consistent with hypopotassemia and left ventricular enlargement, decrease in the levels of serum potassium, and subjective complaints of frequent headache and giddiness.

Summary

1. A case is presented of marked orthostatic hypotension without tachycardia, with clinical findings suggesting a lesion in the hypothalamus involving the vasoconstrictor, cardioaccelerator and diaphoretic centers.

2. Vasoconstrictor sympathomimetic drugs were ineffective in controlling the blood pressure fall in the erect posture in this patient.

* ACTH was supplied by G. D. Searle & Co., Chicago, Illinois.

3. *l*-norepinephrine, ACTH and vasopressor potentiating substances were ineffective in preventing postural fall in blood pressure.

4. Desoxycorticosterone acetate in oil was given over a three year period, with the production of hypertension in the supine position and only partial relief in preventing the orthostatic fall in blood pressure while the patient was in the sitting position.

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EDITORIAL

THE ANTIANEMIC FACTORS CONCERNED IN MACROCYTIC ANEMIAS

THE intensive investigations of the past two decades have not only revolutionized the treatment of the macrocytic anemias, but they have revealed the nature of some of the substances concerned in hemopoiesis and have given at least an indication of some of the biochemical reactions involved.[1] The function of these substances is by no means restricted to maintaining normal hemopoiesis. They are essential for the metabolism of all the body cells and indeed for the life and growth of all classes of living organisms. Much of what is known about them and even the practicable methods for their detection and assay are dependent upon a study of their activity in cultures of suitable species of bacteria.

The first important contribution was furnished by the well known work of Castle and his associates. Some substance present in certain foods such as muscle meat, a thermostable "extrinsic factor," combined with a thermolabile "intrinsic factor" present in normal gastric juice but absent or greatly diminished in pernicious anemia, produces a mixture which brings about normal hemopoiesis when administered orally to patients with pernicious anemia. The reliability of this observation is securely established. The substance directly exerting this effect, the "antipernicious anemia factor," as is well known, is present in relatively high concentration in normal mammalian liver but absent from the liver in severe pernicious anemia.

Intrinsic factor alone is ineffective, however administered. The earlier attempts to secure extracts of extrinsic factor active on parenteral administration were unsuccessful (although this has since been accomplished).[2] It was assumed, therefore, that the active substance in liver was a distinct and different substance, produced by the interaction of the extrinsic and intrinsic factors. Since the activity of incubated mixtures of extrinsic factor and gastric juice is destroyed by heating, whereas the active principle in liver is thermostable, it seemed probable that some elaboration of the latter occurred after absorption, presumably either in the intestinal mucosa or in the liver itself. For this, however, there was no direct proof, since these substances had not been isolated and their chemical composition was not known.

The next major advance was the isolation and synthesis of folic acid (pteroylmonoglutamic acid), although the earlier observations regarding

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this were temporarily confusing.[3] The indispensability of folic acid for normal hemopoiesis and the development of severe macrocytic anemia in its absence are thoroughly established. It was quickly evident, however, that folic acid does not correspond to any of Castle's factors. Since folic acid causes an excellent initial hematological remission in pernicious anemia, it was suggested that folic acid might be the substance directly concerned and that the factor in liver served to make folic acid available in effective form.[4]

In natural foodstuffs folic acid is present largely as conjugates which appear to be inactive until they are split by specific enzymes, conjugases, present in certain body tissues. Such foods supply the need for folic acid in normal persons, but when administered to patients with pernicious anemia they were apparently not adequately utilized. The presence of substances inhibiting these enzymes in foods containing folic acid conjugates casts some doubt on the conclusions which might be drawn from this observation.

It was soon found that folic acid is inert in preventing or arresting the neurologic degenerations in pernicious anemia and sometimes the glossitis. Furthermore folic acid does not maintain a hematologic remission indefinitely. Relapse occurs after a year or more, while under treatment. Although a second briefer remission may often be obtained by a large increase in dose, a "mass action" effect, the appearance of grave neurologic disturbances usually terminates the experiment at this point. Potent liver extract will then arrest the neurologic disturbances promptly.[5] Folic acid, therefore, cannot replace the factor in liver in pernicious anemia, and the primary function of the latter cannot be merely to make folic acid available, although it may also serve to do this.

The isolation of vitamin B_{12} has greatly facilitated these studies by providing another of these substances in pure and identifiable form.[6, 7] It appears to be identical with Castle's extrinsic factor, although it probably may occur in natural sources in the form of conjugates. It has been demonstrated by microbiological assay in the various natural sources of extrinsic factor, and like the latter is very poorly absorbed from the gastrointestinal tract by patients with pernicious anemia unless administered with intrinsic factor.

Vitamin B_{12} is also substantially identical with the active principle of liver. As thus far observed, therapeutically it precisely duplicates the action of potent liver extracts. Both are highly effective on parenteral injection but are poorly absorbed by patients with pernicious anemia unless intrinsic

[3] Jukes, T. H., and Stokstad, E. L. R.: Pteroylglutamic acid and related compounds, Physiol. Rev. **28**: 51-106, 1948.

[4] Welch, A. D., et al.: Ineffective utilization of pteroylglutamic (folic) acid in pernicious anemia, J. Biol. Chem. **164**: 787, 1946.

[5] Vilter, R. W., et al.: Studies on the relationships of vitamin B_{12}, folic acid, thymine, uracil, and methyl group donors in persons with pernicious anemia and related megaloblastic anemias, Blood **5**: 695-717, 1950.

[6] Strauss, M. B.: Vitamin B_{12} and pernicious anemia, New England J. Med. **243**: 187, 1950.

[7] Girdwood, R. H.: Vitamin B_{12} and related factors. A clinical and experimental review, Edinburgh M. J. **57**: 72-109, 1950.

factor is also administered. These observations suggested that extrinsic factor and the liver factor are identical, both vitamin B_{12}, and that intrinsic factor functions solely by making this available,[8] either by protecting it from destruction by intestinal bacteria or more probably by facilitating its absorption. B_{12} is present in significant amounts in the feces in pernicious anemia (about 5 μg. per day), presumably synthesized by intestinal bacteria, but it can not be absorbed by the lower bowel.[9]

There is, however, some evidence that B_{12} does undergo some change during or after absorption. Ternberg and Eakin[10] observed that B_{12} becomes inactive in microbiological assays when incubated with gastric juice, but its activity may be restored by heating or enzymatic digestion which destroys intrinsic factor. Ross[11] found that if B_{12} is given parenterally to patients with pernicious anemia, it can be detected in the circulating blood for a short time in microbiologically active form. The blood then lost this activity, but this could be restored by heating the diluted serum.

Lajtha and associates[12] reached similar conclusions from a study of cultures of bone marrow cells from patients with untreated pernicious anemia. Neither B_{12} nor intrinsic factor separately exerted any effect on these cultures, but in combination they stimulated the maturation of the megaloblasts. Serum of normal subjects exerted a similar effect, whereas serum of untreated cases of pernicious anemia had an inhibitory action. If B_{12} was administered parenterally to such patients, their serum stimulated maturation of the cells, like normal serum. Lajtha concluded that B_{12} must have combined with "intrinsic factor" present in the body tissues or fluids in order to have acquired such activity.

Horigan, Jarrold and Vilter[13] drew contrary conclusions from experiments of a different type. The injection of small doses of B_{12} into the bone marrow in pernicious anemia stimulated a maturation of the cells which was limited to the vicinity of the injection, whereas folic acid and citrovorum factor did not do so in the doses employed.

Both folic acid and citrovorum factor stimulated maturation of the cells in Lajtha's cultures without B_{12}, but this is not surprising in view of the initially potent effect of these substances in vivo.

As in the case of vitamin K, several (at least four) distinct but closely

[8] Berk, L., Castle, W. B., et al.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. X. Activity of vitamin B_{12} as food (extrinsic) factor, New England J. Med. **239**: 911, 1948.

[9] Girdwood, R. H.: The intestinal content in pernicious anemia of factors for the growth of *Streptococcus faecalis* and *Lactobacillus leichmanii*, Blood **5**: 1009-1016, 1950.

[10] Ternberg, J. L., and Eakin, R. E.: Erythein and apoerythein and their relation to the antipernicious anemia principle, J. Am. Chem. Soc. **71**: 3858, 1949.

[11] Ross, G. I. M.: Vitamin B_{12} assay in body fluids, Nature **166**: 270, 1950.

[12] Callender, S. T., and Lajtha, L. G.: On the nature of Castle's hemopoietic factor, Blood **6**: 1234-1239, 1951.

[13] Horrigan, D., Jarrold, T., and Vilter, R. W.: Direct action of vitamin B_{12} upon human bone marrow. The effect of instillation of vitamin B_{12} and folic acid into the bone marrow as studied by nucleic acid staining techniques, J. Clin. Investigation **30**: 31-36, 1951.

related substances exert the activity of the original vitamin B_{12}, which has been termed cyanocobalamine [14] because it contains a cyanide group. In the variants this is replaced by an hydroxyl or a nitrite group or it is eliminated entirely. Although these forms may differ somewhat in microbiological assays, they appear to be equally potent in pernicious anemia and differentiation at present has no therapeutic significance.

Vitamin B_{12} is one of the most potent biochemical substances known. In bacterial cultures it may be active in concentrations of one part in a hundred billion and in man three micrograms may exert a demonstrable effect. One U.S.P. unit of liver extract is equivalent to about 2.3 micrograms. One gram would be ample to secure and maintain an adequate remission for a year in more than a thousand cases of pernicious anemia on a generous dosage.

Less is known regarding the nature of the intrinsic factor. Glass, Boyd et al.[15] isolated from normal gastric juice a "glandular mucoprotein" in relatively pure state, which in doses of 100 to 200 mg. markedly potentiated the effect of B_{12} when administered orally to nine cases of pernicious anemia. It is secreted by the mucous cells in the necks of the glands in the fundus and corpus of the stomach, and its activity corresponded approximately to that expected of the volume of gastric juice from which it was isolated. Its distribution, physical and chemical properties are like those of intrinsic factor. The manner in which it acts (enzymic?) was not demonstrated, but they doubt that it combines stoichiometrically with B_{12}, since within limits an increase in the dose of either substance compensated for a deficiency of the other.

Knowledge concerning the exact rôle these substances play in cellular metabolism is fragmentary, and the current theories are highly speculative. Much of what is known is based on microbiologic assays which are subject to technical errors and are not strictly specific. There is considerable evidence, however, that these substances function as enzymes in the synthesis of nucleic acid.[16, 5] It now seems probable that folic acid is not itself active, but that it furnishes the substrate for the formation of folinic acid, the citrovorum factor. The latter appears to be concerned in an early stage of the synthesis, facilitating the formation of pyrimidines such as thymine from amino acids and other simple materials. B_{12} appears to be active in a later stage, in the synthesis of nucleosides such as thymidine from pyrimidines and purines. Abnormalities in the distribution of ribonucleic acid in the primitive erythroblasts in pernicious anemia have been described.[13]

If a folic acid antagonist like aminopterin is administered to a patient

[14] Brink, N. G., et al.: Vitamin B_{12}—identification as a cyano-cobalt co-ordination complex, Science **112**: 354, 1950.

[15] Glass, G. B. J., et al.: Relationship of glandular mucoprotein from human gastric juice to Castle's intrinsic antianemia factor, Science **115**: 101–108, 1952.

[16] Stokes, J. L.: Substitution of thymine for "folic acid" in the nutrition of lactic acid bacteria, J. Bact. **48**: 201, 1944.

with pernicious anemia, B_{12} is no longer effective.[17] This inhibition is relatively little affected by administering folic acid but is eliminated by citrovorum factor.[18] It seems unlikely that aminopterin has a direct antagonistic effect on B_{12}. It is more probable that it interrupts the chain of reactions at an earlier stage, possibly by preventing the formation of citrovorum factor, thus cutting off the supply of "semifinished products" on which B_{12} operates. Their production would be resumed after citrovorum factor was administered, and B_{12} would then find materials on which its activity can be exerted. Theoretically, therefore, citrovorum factor should be the ideal antidote for aminopterin poisoning.

These relationships are manifestly complex and poorly understood. Both folic acid and B_{12} are required for normal hemopoiesis. Lack of either results in a megaloblastic type of bone marrow and a macrocytic anemia, and neither will adequately compensate for lack of the other. Other substances still inadequately identified, such as possibly the Wills factor, are probably also essential. Norwegian investigators[19] have described in pernicious anemia a diminution of prothrombin, and a macrocytosis associated with a pathologic type of hemoglobin resembling the fetal type, which are not affected by B_{12} or folic acid, singly or in combination, but which revert to normal if crude liver extracts are administered.

From the therapeutic standpoint, B_{12} in any of its forms and potent refined liver extracts are equivalent. B_{12} is highly effective on parenteral injection, and 10 μg. per day is a generous optimum dose during the first week of treatment. Much larger quantities are harmless but wasteful, as up to 98 per cent of the excess may be excreted in the urine within 24 hours. B_{12} given orally is poorly and uncertainly absorbed in pernicious anemia, but if given with adequate intrinsic factor, it is usually effective in a dose five to 10 times the parenteral dose. Parenteral injections are more dependable and preferable whenever feasible. If the diet is reasonably adequate, folic acid does not potentiate B_{12}; it is unnecessary but not harmful. Folic acid alone in pernicious anemia is inadequate and dangerous because of the risk of neurologic degenerations. On the other hand, in the macrocytic anemias resulting from dietary insufficiency, pregnancy, sprue and other disturbances of intestinal absorption, in which neurologic degenerations almost never occur, folic acid may be highly effective, even in some cases which are refractory to B_{12}. An accurate diagnosis is obviously essential for the rational treatment of these disorders. The precipitate administration of these potent agents before a diagnosis has been made makes this virtually impossible later.

P. W. C.

[17] Meyer, L. M., et al.: Studies in pernicious anemia patients treated with liver extract and folic acid antagonists, Am. J. M. Sc. **218**: 197, 1949.

[18] Ellison, R. R., et al.: Effect of citrovorum factor in pernicious anemia, Proc. Soc. Exper. Biol. and Med. **76**: 366, 1951.

[19] Owren, P. A.: Is B_{12} the complete therapeutic answer in pernicious anemia? Proc. Internat. Soc. Hematology, Third Congress, Aug. 21–25, 1950–1951, Grune and Stratton, New York, p. 22–24.

REVIEWS

Nerve Impulse: Transactions of the First Conference, March 2–3, 1950, New York, N. Y. Editor: DAVID NACHMANSOHN. 159 pages; 15.5 × 23.5 cm. Josiah Macy, Jr. Foundation, New York. 1951. Price, $3.00.

The Macy Foundation is breaking new scientific ground in its Conference Program, which now includes thirteen discussion groups. Dr. Frank Fremont-Smith, its Medical Director, indicates the objective of this program in his description of the purpose of this first meeting of the group studying the nerve impulse.

The Foundation is interested not only in furthering knowledge concerning the nerve impulse, but also in investigating the broad aspects of the problem of communication and of integration. . . . One of the greatest needs today is a reintegration of science, now artificially fragmented by the isolation of the several disciplines or specialties."

In order to further this reintegration of science the study group brings together a small number of experts interested in (1) the electrical and physical aspects of nerve activity, presented by Dr. Harry Grundfest, (2) the biochemical approach to the problem, discussed by Dr. J. H. Quastel, (3) the contributions of comparative physiology, reviewed by Dr. C. Ladd Prosser, (4) the results of histological studies, described by Dr. David Bodian, and (5) the permeability of the nerve membrane for ions, outlined by Dr. Henry B. Steinbach. In each section of the subject discussion quickly becomes general, with question and answer in the manner of the Socratic dialectic. Much of the flavor of the original give and take is preserved in the report, but there are notable lapses. Although the editor had opportunity to smooth the English by later consultation with the participants, the argument often becomes decidedly rough-and-tumble, with questions asked that have no answers, and answers given to questions which have disappeared from the text. A further element of confusion is caused by a regrettable number of solecisms.

In spite of these blemishes, partly inseparable from extemporaneous scientific speech, the argument has power and life. The reader is carried through vigorous discussions of a long array of topics. They include a consideration of the reliability and limitations of electronic instrumentation, of the modification of phenomena in the very process of study, of spontaneous activity in single nerve cells, and of synchronization of activity in groups of cells, of the use of intracellular electrodes, by which the action potential is shown to be greater than the injury potential, of the rôle of the sodium ion in causing this reversal of potential across the nerve membrane during activity, of the enzyme systems of nerves and the effect of drugs upon them, of the rôle of acetylcholine and of vitamins in conduction, and in transmission across the synapse, of centralization and cephalization in invertebrate nervous systems, and the development in them of summation, facilitation and inhibition, of nerve cell topography and internal structure, with discussion of the rôle of nodes of Ranvier in "saltatory" conduction, of types of synaptic junctions, and of the mechanism of ion movement through the membrane, and accumulation within the nerve cell.

In his own contributions to the discussions the editor intimates that the concept of chemical transmitters of activity from cell to cell has been abandoned. The reader should be warned that many investigators, including some members of this discussion group, have not forsaken the original Loewi viewpoint. It has, indeed, been strongly supported by some recent work, such as the studies of J. C. Eccles.

W. R. AMBERSON

Endocrine Functions of the Pancreas. By BERNARD ZIMMERMAN, M.D., Department of Surgery, University of Minnesota, Minneapolis, Minn. 82 pages; 14.5 × 22.5 cm. (limp leather binding). Charles C Thomas, Springfield, Illinois. 1952. Price, $2.50.

The established and proposed hormones of the pancreas are discussed in a concise review of the major contributions to the subjects.

Regarding insulin the discussion includes the metabolism in diabetes, the action of insulin and the control of insulin release from the pancreas. The various classical differences of points of view are represented.

The lipotropic factors of the pancreas are briefly considered also with presentation of the conflicting viewpoints. The upshot is fairly well represented by the statement that "few people have accepted the idea that the lipotropic factor of the pancreas is an internal secretion." The probable importance of the enzymes of the external secretion in liberating known lipotropic agents from the food is mentioned.

The section on the hyperglycemic factor of the pancreas is particularly timely. Probability exists, however, that lack of the external secretion of the pancreas deserves more consideration as a cause of the apparently low insulin requirement of the depancreatized subject.

The book is very short, containing only 78 pages of which 19 are bibliography. The book has a particular usefulness as a key to these references. Typographical errors are unusually few. CO_2 appears instead of the intended O_2 in the chemical equation on page 17.

G. E. G.

The Care of the Ageing and Chronic Sick. By A. P. THOMSON, M.C., M.D., Ch.B. (Birmingham), F.R.C.P. (London), Dean of the Faculty of Medicine and Professor of Therapeutics, University of Birmingham, etc.; C. R. LOWE, M.D., Ch.B. (Birmingham), M.R.C.S. (England), L.R.C.P. (London), D.P.H., Lecturer in Public Health, Department of Social Medicine, University of Birmingham, and THOMAS MCKEOWN, B.A. (British Columbia), Ph.D. (McGill), D.Phil. (Oxford), M.D. (Birmingham), M.B., B.S. (London), Professor of Social Medicine, University of Birmingham, etc. 133 pages; 25 × 17 cm. (paper-bound). 1951. Published for the Birmingham Regional Hospital Board by E. & S. Livingstone, Ltd., Edinburgh and London. Price, $1.50.

There is a rapidly growing literature in this country, both popular and professional, which attests to the recognition accorded to the problems presented by our aging population. These problems are of a more acute nature in England, and in that country some very interesting experiments in the medical care of the aging and chronically ill have been inaugurated. Dr. Thomson, as Chairman of the Planning Committee of the Birmingham Regional Hospital Board, has published in this small volume some of the results of a survey of the problem in the Birmingham area and the conclusions which have been reached. Many of the conditions found in the homes and in the hospitals for chronic illness in the Birmingham area would be applicable to larger American cities.

The contents of the book have been previously published as separate papers in the *British Medical Journal* or the *British Journal of Social Medicine* in 1949 and 1950. There are included Professor Thomson's Lumleian Lectures on Problems of Ageing and Chronic Sickness, and five separate papers on special aspects of the survey.

One is impressed by the intensely practical point of view pervading the report. The humanitarian obligations for provision of care are accepted without discussion and the inquiry is directed at the problems of where and how: in the family home;

in special housing; in long stay wards; in acute wards. The discussion of these possibilities, based on the data of the survey, is of great interest. It is not possible to present it in a brief review. The following quotations may be of interest:

"In these debatable matters a decision requiring high qualities of statesmanship is necessary before new plans are made to deal with the problems of the chronic sick and infirm. The problem is simple. Shall they become the responsibility of society in large institutions or should we encourage their friends and their families to care for them whenever possible? . . . For all these reasons and to avert the distressing disintegration of human personality that is so common in patients who lie for years in an infirmary it would be wiser to preserve the sense of family responsibility and to encourage people to tend their own sick and guard the aged.

"That does not mean that families should be expected to bear the whole burden. Society must help them and the problem really hinges on the type and extent of assistance to be provided."

M. C. P.

I; *for Medical Writing:* A Useful Guide to Principles and Practice of Effective Scientific Writing and Illustration. By EDWIN P. JORDAN, M.D., and WILLARD C. SHEPARD. 112 pages; 15.5 × 23.5 cm. W. B. Saunders Co., Philadelphia. 1952. Price, $2.50.

Today it is difficult to find a medical article that is not blemished by one or more of the following—medical jargon, verbosity, technical superfluities, misspelling, repetitiousness or "verbicide." This little book will help to eliminate these and other flaws and should sharpen the critical faculties of would-be writers.

The question of medical writing presents an unfortunate paradox. The powers controlling the policies of medical departments are often stridently insistent that their protégés give birth to a steady stream of publications. Yet how many of them allot time in their curricula for much-needed instruction in the gentle art of writing? The unhappy result is that many of these forced births are literary monsters. If so much writing is so important (which is doubtful) then *writers should be trained.* For, as the authors aptly point out in their preface, "good writing is only one part inspiration and nine parts perspiration."

There are chapters on the preliminaries, the first draft, the first, second and third revisions, the beginning and the end, special problems, making the index, illustrations and statistics employed in medical papers. Some useful appendices follow including a table of proofreaders' marks, common abbreviations, useful equivalents and a table of X^2 probability scale.

In the early chapters the authors emphasize some excellent points. They encourage the 5″ by 8″ card habit, the liberal use of subheadings, the use of the first person singular where that is what is meant (rather than false modest circumlocutions or the royal "we"), and the common rather than the polysyllabic word. They favor at least four revisions ("easy reading was hard composing"), and they rightly extol the value of reading the manuscript aloud. They condemn many of the common villainies of modern writing—the long paragraph, summaries that fail to summarize, the verbatim quotation of reports from clinical and pathological laboratories, and the needless duplication in the text of tabulated material. They deplore the habit of entrusting the preparation of references to secretary or librarian and the prevalent epidemic of "rehashes" of information previously published.

These and numerous other valuable points of style and practice are lucidly stressed in the opening chapters. Good as these sections are, they would be of even greater value if they were somewhat expanded to include more examples of the points the authors are expounding; too often the advice is left as a general precept without adequate illustration.

The chapter on statistics is excellent, but it would be enhanced by a few lines of detailed instruction on how to use the table of X^2 probability scale. It is impossible to follow the argument on pages 76 and 77 without knowledge of this table's use, and this is undoubtedly not as self-evident to the humble medico as to the statistician. The section on illustrations is interesting and helpful, but it is unnecessarily detailed.

This book is easy to read and enticingly brief. If a large number of aspirants to medical "literature" are successfully tempted to read these pages and obey the excellent and timely advice therein contained, the editors and readers of medical journals will alike have much to be thankful for.

H. J. L. M.

A Course in Practical Therapeutics. 2nd Ed. By MARTIN EMIL REHFUSS, M.D., F.A.C.P., and ALISON HOWE PRICE, A.B., M.D. 938 pages; 22.5 × 29 cm. Williams and Wilkins Company, Baltimore. 1951. Price, $15.00.

This textbook of therapeutics was developed by a group of members of the faculty of the Jefferson Medical College of Philadelphia, under the leadership of Dr. Rehfuss, for the medical student and the general practitioner. Seventeen contributions are listed, but sections are not credited to individual authors.

The book is divided into four major parts. The first discusses general therapeutics, including definite plans of therapy, prescription writing, nursing care and diet. The second section, of 110 pages, takes up the problems of symptomatic therapy, and the third, by far the largest division, includes the management of specific disease states.

The chapter on special therapeutic methods, pages 755 to 910, discusses problems not covered previously, and includes pre- and postoperative care, parenteral treatment, pediatrics and radiation therapy.

In general, the textbook makes a very favorable impression. It is a large, handsome volume, though probably too bulky, as it weighs six and three-quarters pounds. Much of the excess weight is the result of inclusion of 96 full page illustrations, many of whose value is questionable. Duplication of information in different sections is also a handicap. For example, digitalis is discussed on pages 106 to 110, in the "symptomatic therapy" section, under the management of edema. It is again discussed on pages 362 to 364, in the "specific disorder" section on heart disease. Treatment of tetany takes up a full page in the therapy of convulsions, and another two pages later, under the heading "Tetany." Other examples of duplication can be found.

There is no doubt that writing or editing a textbook of therapeutics is one of the most difficult tasks that can be undertaken by the medical author. There is also no doubt that Dr. Rehfuss and his group have made a valuable contribution to our library of textbooks.

T. N. C.

Hippocrates on Intercourse and Pregnancy. An English Translation of *On Semen and on the Development of the Child.* By TAGE U. H. ELLINGER, Sc.D., M.A.; with an introduction by ALAN F. GUTTMACHER, M.D. 128 pages; 11 × 16 cm. Henry Schuman, Inc., New York. 1952. Price, $2.50.

This is the first English translation of one of the lesser known Hippocratic works. Although most scholars agree that it was not written by Hippocrates of Cos but was probably written by someone in the Cnidian school, it is agreed that it was written in the fifth century B.C. The book gives a clear statement of the current theories of reproduction, embryology and heredity. The author applied the scientific method and described in detail his experiments in chick embryology. The translation is

scholarly and clear. The value of the book is enhanced by an Introduction and a series of Notes by Dr. Alan F. Guttmacher, Associate Professor of Obstetrics at the Johns Hopkins University. Anyone who is interested in the history of the medical sciences will find this book to be an asset in his library.

H. W. N.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Any Questions? A Selection of Questions and Answers Published in the British Medical Journal. First Series. 240 pages; 19 × 12 cm. 1951. Grune & Stratton, Inc., New York. Price, $2.50.

Arterielle Therapie. By PROF. DR. G. JORNS. 140 pages; 24.5 × 17.5 cm. 1950. Walter de Gruyter & Co., Berlin. Price: Gzl. DM 14.–

Cardiac Emergencies and Heart Failure: Prevention and Treatment. By ARTHUR M. MASTER, M.D., Cardiologist, Mount Sinai Hospital, New York, N. Y.; MARVIN MOSER, M.D., 1st Lt., USAF(MC) Walter Reed Army Hospital, Washington, D. C., etc., and HARRY L. JAFFE, M.D., Adjunct Physician, Cardiology, Mount Sinai Hospital, New York, N. Y. 159 pages; 20.5 × 14 cm. 1952. Lea & Febiger, Philadelphia. Price, $3.00.

Current Therapy, 1952. Latest Approved Methods of Treatment for the Practicing Physician. Editor: HOWARD F. CONN, M.D. Consulting Editors: M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, WILLIAM J. KERR, PERRIN H. LONG, H. HOUSTON MERRITT, PAUL A. O'LEARY, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS and ROBERT H. WILLIAMS. 849 pages; 27.5 × 20 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $11.00.

Diagnostic and Experimental Methods in Tuberculosis. 2nd Ed. By HENRY STUART WILLIS, M.A., M.D., F.A.C.P., Superintendent and Medical Director, North Carolina Sanatoria, McCain, North Carolina, etc.; and MARTIN MARC CUMMINGS, M.D., F.C.C.P., Director, Tuberculosis Research Laboratory, Lawson Veterans Administration Hospital, Veterans Administration, Chamblee, Georgia, etc. 373 pages; 24 × 16 cm. 1952. Charles C Thomas, Publisher, Springfield, Illinois. Price, $10.00.

XI Conférence de L'Union Internationale Contre la Tuberculose, Copenhague, 3–6 Septembre 1950, Association Nationale Danoise Contre la Tuberculose Copenhague. 734 pages; 26 × 17.5 cm. 1951. NYT Nordisk Forlag, Arnold Busck, Copenhagen.

Food and Nutrition. 2nd Ed. By E. W. H. CRUICKSHANK, M.D. (Aberd.), D.Sc. (Lond.), Ph.D. (Cantab.), M.R.C.P., Regius Professor of Physiology in the University of Aberdeen. 443 pages; 22 × 14 cm. 1951. The Williams & Wilkins Company (A William Wood Book), Baltimore. Price, $6.50.

Grundlagen der Strahlentherapie: Physik, Biologie und allgemeine Therapie. By DR. MED. RICHARD KURT KEPP, with a Foreword by PROF. DR. HEINRICH MARTIUS. 357 pages; 25 × 17 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 38.–

Joll's Diseases of the Thyroid Gland. 2nd Ed. By FRANCIS F. RUNDLE, M.D., F.R.C.S., The Unit of Clinical Investigation, The Royal North Shore Hospital of Sydney, Australia, etc. 520 pages; 24.5 × 18.5 cm. 1951. Grune & Stratton, Inc., New York. Price, $12.75.

Die Krankhafte Blutdrucksteigerung. By PROF. DR. L. HANTSCHMANN. 228 pages; 24.5 × 18 cm. 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 36.–

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER. 2,884 pages; 28 × 20 cm. (paper-bound). 1952. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, DM 98.–

Leonardo da Vinci on Movement of the Heart and Blood. By K. D. KEELE, M.D., F.R.C.P.; with a Foreword by CHARLES SINGER, M.D., F.R.C.P. 142 pages and 68 plates; 24 × 18.5 cm. 1952. J. B. Lippincott Company, Philadelphia. Price, $15.00, limited numbered edition, 500 copies only available.

Medical Certification of Cause of Death: Instructions for Physicians on Use of International Form of Medical Certificate of Cause of Death. Bulletin of the World Health Organization, Supplement 3. 20 pages; 24 × 16 cm. (paper-bound). 1952. World Health Organization; available from Columbia University Press, International Documents Service, 2960 Broadway, New York 27. Price, 20¢.

The Musculoskeletal System: A Symposium Presented at the Twenty-third Graduate Fortnight of the New York Academy of Medicine, October Ninth to Twentieth, 1950. Edited by MAHLON ASHFORD, M.D. 368 pages; 22 × 14.5 cm. 1952. The Macmillan Company, New York. Price, $6.50.

The Pathology of Diabetes Mellitus. 3d Ed. By SHIELDS WARREN, M.D., Sc.D., Departments of Pathology of the New England Deaconess Hospital and the Harvard Medical School, Boston, Massachusetts, etc.; and PHILIP M. LECOMPTE, M.D., Departments of Pathology of the Faulkner Hospital and the Harvard Medical School, Boston, Massachusetts. 336 pages; 24 × 15.5 cm. 1952. Lea & Febiger, Philadelphia. Price, $7.50.

Preventive Medicine and Public Health. 2nd Ed. By WILSON G. SMILLIE, A.B., M.D., D.P.H., Sc.D. (Hon.), Professor of Public Health and Preventive Medicine, Cornell University Medical College, New York, N. Y. 603 pages; 24 × 16 cm. 1952. The Macmillan Company, New York. Price, $7.50.

Progress in Allergy. Volume III. Contributors: J. F. ACKROYD, London; R. BIRCHER, Basel; E. A. BROWN, Boston, Mass.; W. HADORN, Bern; J. HARKAVY, New York, N. Y.; D. HARLEY, London; L. KALLÓS-DEFFNER, Helsingborg; M. M. PESHKIN, New York, N. Y.; E. ROTHLIN, Basel; A. H. ROWE, Oakland, California; A. STOLL, Basel; L. UNGER, Chicago, Ill., and F. WYSS, Bern; edited by PAUL KALLÓS, Helsingborg. 572 pages; 24.5 × 17.5 cm. 1952. S. Karger, Basel; available in U. S. A. through Interscience Publishers, Inc., New York. Price, $16.50.

Recent Advances in Clinical Pathology. 2nd Ed. By VARIOUS AUTHORS. General Editor: S. C. DYKE, D.M. (Oxon), F.R.C.P. (Lond.); Section Editors: Bacteriology: R. CRUICKSHANK, M.D. (Aberd.), F.R.C.P. (Lond.); Biochemistry:

E. N. Allott, D. M., B.Sc. (Oxon), F.R.C.P. (London); Haematology: R. G. MacFarlane, M.D. (Lond.); Histology: A. H. T. Robb-Smith, M.D. (Lond.), M.R.C.P. (Lond.). 575 pages; 21 × 14 cm. 1951. The Blakiston Company, Philadelphia. Price, $6.00.

Signs and Symptoms: Applied Pathologic Physiology and Clinical Interpretation. 2nd Ed. Edited by Cyril Mitchell MacBryde, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine, etc. 783 pages; 23.5 × 15.5 cm. 1952. J. B. Lippincott Co., Philadelphia. Price, $10.00.

Spatial Vectorcardiography. By Arthur Grishman, M.D., Adjunct Physician for Cardiology, The Mount Sinai Hospital, New York, etc.; and Leonard Scherlis, M.D., Research Assistant in Cardiology, The Mount Sinai Hospital, New York. 217 pages; 28.5 × 20.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $6.00.

Steps Toward Prevention of Chronic Disease: Summary of the National Conference on Chronic Disease: Preventive Aspects, Held March 12–14, 1951. Sponsor: Commission on Chronic Illness. Co-sponsors: U. S. Public Health Service, National Health Council. 31 pages; 25.5 × 17.5 cm. (paper-bound). 1952. Health Publications Institute, Inc., Raleigh, N. C. Price, 1–9 copies, 50¢ each; 10–49 copies, 45¢ each; 50–99 copies, 40¢ each; 100 or more copies, 35¢ each.

A Symposium on Essential Hypertension: An Epidemiologic Approach to the Elucidation of Its Natural History in Man. A State Document of the Commonwealth of Massachusetts, Published under Special Legislative Act. 373 pages; 23.5 × 15.5 cm. 1951. Distributed by the Secretary of the Commonwealth, Room 116, State House, Boston 33. Price, $3.95.

A Textbook of Orthopedics, with a Section on Neurology in Orthopedics. By M. Beckett Howorth, M.D., Clinical Professor of Orthopedic Surgery, New York University Post-Graduate Medical School, etc.; in association with Fritz J. Cramer, M.D., A. Wilbur Duryee, M.D., Donovan J. McCune, M.D., J. William Littler, M.D., and Walter A. Thompson, M.D. 1,110 pages; 25.5 × 16.5 cm. 1952. W. B. Saunders Company, Philadelphia. Price, $16.00.

COLLEGE NEWS NOTES

The College is gratified to announce the following new Life Members:

Dr. Leonard Horn, Rochester, N. Y.
Dr. Frank S. Horvath, Washington, D. C.
Dr. Charles F. Stone, Jr., Atlanta, Ga.
Dr. Howard Osgood, Buffalo, N. Y.
Dr. Saul D. Rotter, West Palm Beach, Fla.
Dr. Vincent W. Koch, Janesville, Wis.
Dr. Abraham Judah Kauvar, Denver, Colo.
Dr. John H. Foster, Waterbury, Conn.
Dr. Elbert L. Persons, Durham, N. C.
Dr. Frederick R. Lummis, Houston, Tex.
Dr. Charles D. Reece, Houston, Tex.
Dr. Harry F. Klinefelter, Jr., Baltimore, Md.

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1953–June 30, 1954. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $3,000 to $3,500.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than October 1, 1952. Announcement of awards will be made November, 1952.

Coming Certifying Board Examinations

American Board of Internal Medicine, William A. Werrell, M.D., Secretary Treasurer, 1 W. Main St., Madison 3, Wis.

Written examinations—October, 1952, various centers.

Oral examinations: Chicago, Ill., June 5, 6, 7, 1952; San Francisco, Calif., September or October, 1952; New York, N. Y., November or December, 1952; New Orleans, La., February 3, 4, 5, 6, 1953; Atlantic City, N. J., April, 1953 (during week preceding American College of Physicians meeting); New York, N. Y., May, 1953 (during week preceding American Medical Association Meeting).

American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Oral examinations—San Francisco, Calif., June 27, 28, 29, 1952.

American Board of Physical Medicine and Rehabilitation, Robert L. Bennett, M.D., 30 N. Michigan Ave., Chicago 2, Ill.

Written and oral examinations—Chicago, Ill., June 8 and 9, 1952.

Postgraduate Course in Psychiatry and Neurology

The University of California School of Medicine announces a postgraduate course in psychiatry and neurology at the Langley Porter Clinic, August 25–October 31, 1952, the course being given in coöperation with University Extension (Medical Extension), University of California. The course is open only to qualified physicians. It will be given under the direction of Dr. Karl M. Bowman, Professor of Psychiatry, with the assistance of staff members from the various divisions of the Medical School. The course will include a general review of psychiatry and neurology, with material from related fields in medicine. It is particularly designed to prepare psychiatrists and neurologists for the examinations of the American Board of Psychiatry and Neurology. It is therefore designed for the advanced student, rather than the beginner. A special endeavor will be made to present the latest knowledge and advances so as to make the student familiar with the most recent developments in this field. The tuition fee is $200.00 payable in advance. For application form and other data, send inquiries to:

Stacy R. Mettier, M.D., F.A.C.P.
Professor of Medicine
Head of Postgraduate Instruction
Medical Extension
University of California Medical Center
San Francisco 22, Calif.

Conference Committee on Graduate Training in Medicine

The Conference Committee on Graduate Training in Medicine is a coöperative Committee with two representatives each from the American College of Physicians, the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. Its chief function is the approval of hospitals for residency training in internal medicine. The members of the Committee are as follows:

From the Council on Medical Education and Hospitals:

Russell L. Haden, M.D., Chairman, Crozet, Va.
Francis C. Wood, M.D., Philadelphia

From the American College of Physicians:

LeRoy H. Sloan, M.D., Chicago
Alex. M. Burgess, Sr., M.D., Providence

From the American Board of Internal Medicine

Walter L. Palmer, M.D., Chicago
Roy W. Scott, M.D., Cleveland

A program of clinical traineeships in the prevention, diagnosis, and treatment of arthritis and the metabolic diseases has been established at the National Institute of Arthritis and Metabolic Diseases by the Surgeon General of the Public Health Service. The purpose of the first group of awards is to improve the competency of physicians in the treatment and rehabilitation of arthritis patients.

Applicants must not be over 40 years of age, must be American citizens, graduates of an approved medical school, and have completed a one-year internship in an ap-

proved hospital. The stipend for trainees without dependents is $3,000 per year; with dependents, $3,600. Trainees are placed in qualified institutions of their choice.

For additional information and application forms, write to Chief, Extramural Programs, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Maryland.

The Kappa Delta Award for Research in Orthopaedic Surgery

A prize of $1,000 donated by the Kappa Delta Sorority may be awarded annually by the American Academy of Orthopaedic Surgeons for the best research related to orthopaedic surgery and performed by an American citizen in the United States. This research must be presented to the Committee on Scientific Investigation of the American Academy of Orthopaedic Surgeons before November 1, 1952. Researchers interested in competing for this prize are requested to secure further information from Dr. Claude N. Lambert, 104 South Michigan Ave., Chicago 3, Ill., Chairman of the Award Committee for 1952.

The Society for Investigative Dermatology

The Society for Investigative Dermatology will hold its thirteenth Annual Meeting at the Hotel Sherman, Chicago, Ill., June 7–8, 1952, under the Presidency of Dr. Samuel M. Peck of New York City. Dr. Herman Beerman, F.A.C.P., Philadelphia, is the Secretary-Treasurer.

Future Meetings, American Hospital Association

The American Hospital Association announces the dates and cities for the next four years:

1952—September 15–18—Philadelphia, Pa.
1953—August 31–September 3—San Francisco, Calif.
1954—September 13–16—Chicago, Ill.
1955—September 19–22—Atlantic City, N. J.

The Fourth Inter-American Congress of Radiology will be held in Mexico City on November 2–8, 1952. The address of the headquarters of the Congress is Londres No. 13, Mexico 6, D. F.

The Program Committee has selected two official subjects for this Congress: 1. Radiological Diagnosis of Intra-abdominal Tumors, Other Than Gastrointestinal; and 2. Radiotherapy of Lymphoblastomas (Lymphosarcoma, Hodgkin's Disease, Leukemias).

The Committee also extends an invitation to radiologists in the United States to offer papers on any topic, twenty minutes being allowed for each presentation. For further information, Dr. James T. Case, Chairman of the American delegation, should be addressed at 2315 Bath St., Santa Barbara, Calif.

The International Congress of Physical Medicine is to be held in London, England, July 14–19, 1952. Applications for the Provisional Programme should be addressed to Dr. A. C. Boyle, Honorary Secretary, International Congress of Physical Medicine (1952) 45, Lincoln's Inn Fields, London, W. C. 2.

Clinical medicine for generations was based largely on the study of anatomic and histopathologic material. In recent times the physiological and biochemical approach has supplemented this morphological background. The intensive interest and progress in diseases of nutrition has been largely a development of the physiological and biochemical age. Advancement in the understanding of these disturbances was so great that little attention was paid to the lack of morphological data. Nutrition as a branch of medicine has achieved a permanent place. To complete this maturation of the new science it is important to study the histopathology of the nutritional disturbances. To this end a Registry of Pathology of Nutritional Diseases has been founded. This Registry is sponsored by the American Institute of Nutrition.

The Registry of Pathology of Nutritional Diseases is a unit of the American Registry of Pathology of the Armed Forces Institute of Pathology in Washington, D. C. and is under the auspices of the Committee on Pathology of the National Research Council.

The purposes of the Registry are to provide for the accumulation and maintenance of collections of pathologic materials and related case records in such special fields of nutritional diseases in which it is anticipated that unknown diagnostic and prognostic criteria as well as evaluations of various methods of treatment can be discovered and established through morphologic studies.

The Registry will provide consultation service in the field of nutritional pathology and prepare teaching material in such form as may be most readily and satisfactorily available for loan to qualified students and institutions.

The coöperation of all individuals and institutions is invited. The Registry has been authorized to receive any documented material sent by physicians, hospitals, laboratories or other reliable sources. For further information write to Dr. Herbert Pollack, 70 East 77th St., New York City, or to the Registry of Nutritional Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.

The forthcoming publication of a new international bimonthly is announced by The Nutritional Press of Emmaus, Pa., called *The Journal of Clinical Nutrition.* It will be devoted to "the practical application of the newer knowledge of nutrition," and will feature original papers, review articles, and an integrated abstract section. The Editorial Board consists of: Dr. William Dock, F.A.C.P., N. Y., Dr. Grace M. Goldsmith, F.A.C.P., New Orleans, Dr. Harold Jeghers, F.A.C.P., Washington, D. C., Dr. Robert M. Kark, F.A.C.P., Chicago, Dr. M. M. Wintrobe, F.A.C.P., Salt Lake City, Dr. Michael G. Wohl, F.A.C.P., Philadelphia, Dr. John B. Youmans, F.A.C.P., Nashville, and Dr. S. O. Waife (Associate), Philadelphia, Editor-in-Chief. Among the members of the Advisory Board are I. S. Ravdin, M.D., Paul Gyorgy, M.D., Barnett Sure, Ph.D., H. M. Zimmerman, M.D., Pauline B. Mack, Ph.D., Lester W. Burket, M.D., D.D.S., Charles L. Brown, M.D., F.A.C.P., and P. H. Belding, D.D.S.

Dr. Henry L. Bockus Receives Strittmatter Award

Dr. Henry L. Bockus, F.A.C.P., was the recipient of the 1951 Strittmatter Award of the Philadelphia County Medical Association. The presentation of the traditional gold medal and scroll was made April 9 in Philadelphia. Dr. Bockus' citation read: "for his conspicuous interest and achievements in graduate medical education which have received recognition from his colleagues and students in the United States and many other countries of the world."

Established in 1923 by a past president of the Philadelphia County Medical Society, the Award pays recognition to "any physician making a valuable contribution

to the healing art, including remedial measures, surgical, medical, or contribution to one of the fundamental sciences of medicine having a beneficial influence on either surgery or medicine, or for any extraordinary meritorious service redounding to the credit of the medical profession."

Dr. Bockus, who is Chairman of the Department of Internal Medicine and Gastroenterology at the University of Pennsylvania Graduate School of Medicine, is the fourteenth member of the College to receive this award, which has been made 29 times.

Aero Medical Association Honors Dr. Kenneth Austin Evelyn

The Aero Medical Association honored Dr. Kenneth Austin Evelyn, F.A.C.P., of Montreal, Canada, at its twenty-third annual meeting held in Washington, D. C., March 17–19. He was the recipient of the Theodore C. Lyster Award for "outstanding contributions in the general field of Aviation Medicine." Dr. Louis H. Bauer, F.A.C.P., was presented with specially embroidered Flight Surgeons' wings by the retiring President of the Association, Major General Harry G. Armstrong, F.A.C.P., The Surgeon General, U. S. Air Force. Dr. Bauer, a Flight Surgeon for many years, founded the Association. At the meeting, Dr. Jan H. Tillisch, F.A.C.P., of Rochester, Minn., was elected to the Executive Council; and Commander Harold A. Smedal, (M.C.), U. S. Navy, an Associate of the American College of Physicians, was one of the eight new Fellows elected.

Edwin L. Crosby, M.D., Elected Executive Director, Joint Commission on Accreditation of Hospitals

Dr. Edwin L. Crosby, Adjunct Professor of Public Health Administration at Johns Hopkins University and Director of the Johns Hopkins Hospital, has been appointed Executive Director of the newly formed Joint Commission for the Accreditation of Hospitals and will assume his duties at Chicago on September 1, 1952.

Dr. Crosby was born at Rochester, N. Y., August 18, 1908, received his A.B. degree from Union College, 1929, his M.D. degree from Albany Medical College in 1933, his M.P.H. degree in 1936, and the degree of Dr.P.H. in 1937 from the Johns Hopkins University School of Hygiene and Public Health.

Among his past appointments are: Assistant to Superintendent, Ellis Hospital, Schenectady, N. Y., 1933–34; Epidemiologist-in-Training, New York State Department of Health, Albany, 1935–36; Assistant District Health Officer, New York State Department of Health, Albany, 1936–39; Statistician and Supervisor of Records, 1937–41, Assistant Director, 1941–46, Director, 1946–52, The Johns Hopkins Hospital, Baltimore; Instructor in Biostatistics, 1936–38, Associate in Biostatistics, 1938–45, Assistant Professor of Biostatistics, 1945–48, Associate in Preventive Medicine, 1939–45, Assistant Professor of Preventive Medicine, 1945–46, and Adjunct Professor of Public Health Administration, 1947–52, The Johns Hopkins University.

He is a member of the American College of Hospital Administrators, American Hospital Association, American Medical Association, American Public Health Association, American Statistical Association, Baltimore City Medical Society, Baltimore Hospital Conference (President, 1948–49), Biometric Society, Medical Administrators Conference, Medical and Chirurgical Faculty of Maryland, Society of Medical Administrators, and others. He is also a member of the Health Resources Advisory Committee of the Office of Defense Mobilization and Selective Service, Maryland Advisory Committee of Vocational Rehabilitation, Maryland Hospital Service, Maryland State Planning Commission, and the Salvation Army Advisory Board. He is a

Diplomate of the American Board of Preventive Medicine and Public Health and a Consultant to the Surgeon General, War Department, the Surgeon General of the U. S. Public Health Service and the Medical Director of the Veterans Administration. He is presently President-Elect of the American Hospital Association.

Additional Army Medical Reservists Included in Supplemental Call to Active Duty

Two hundred and six-five officers of the Army Medical Service Reserve will be ordered into active military service in July, the Department of the Army has announced. This is in addition to the original call up of 290 officers made in March. Quotas have been assigned to each of the six Army areas in the continental United States, as well as U. S. Army, Pacific, and U. S. Army, Caribbean.

Under the law, Priority I registrants are defined as those educated at Government expense and others deferred from service to pursue a medical or dental education, who spent less than 90 days on active service in World War II following their training. Priority II registrants differ only in that they have spent more than 90 days but less than 21 months on active service in World War II following their training.

However, the Army is selecting those with the least amount of creditable service first, and no one with more than 12 months of previous service will be called. Physicians and veterinarians will continue to be selected entirely from the Volunteer Reserve, classified as Priority I.

Medical officers selected will be ordered into the active military service for a maximum period of two years.

Army Selects 146 Senior Medical Students for Intern Program

Appointment of 146 senior medical students for the Military Intern Program of the Army Medical Service has been announced by Major George E. Armstrong, F.A.C.P., Army Surgeon General.

The Program, scheduled to get under way July 1, provides that medical students, upon graduation, can be commissioned as first lieutenants in the Medical Corps Reserve and serve their internships in Army hospitals.

Representing 51 medical schools and colleges, the students will be assigned to the ten Army teaching hospitals in the United States and to Tripler Army Hospital in Hawaii. Ninety-eight of those selected, including the three women in the group, have previously served in the armed forces.

In applying, each student was allowed to indicate three hospitals, in order of preference, in which he desired to receive his internship. General Armstrong stated that 75 per cent of the students have been assigned to the first hospital of their choice.

Dr. Jacob Casson Geiger, F.A.C.P., Director of Public Health, was honored by the San Francisco Medical Society on Wednesday, March 12, and was granted an Honorary Fellowship, the first in medical history given to a health officer. Dr. Geiger retired March 1 as Director of Public Health, City and County of San Francisco. The citation read: "For scientific acumen in the successful handling for 21 years of Public Health problems of a large city, San Francisco."

Dr. Walter M. Boothby, F.A.C.P., Professor Emeritus of the Mayo Foundation and head of the respiratory laboratory of the Lovelace Foundation for Medical Education and Research in Albuquerque, N. M., was recently awarded the Order of Com-

mander of the North Star by the Crown of Sweden. Dr. Boothby, who received the award from the Swedish Consul in Houston, Texas, at ceremonies held in Albuquerque, helped establish an aeromedical laboratory in Sweden, and has been prominent for many years because of his studies in the field of aviation physiology.

Captain John Ryer Poppen, (M.C.), U. S. N., Retired, F.A.C.P., received the John Jeffries Award at the honor night dinner of the Institute of Aeronautical Sciences, held Jan. 28 in New York City. The second Naval Medical Officer to be so honored, Capt. Poppen was responsible for research in connection with acceleration and its effects on pilots, which led to the development of the G-suits currently worn by Naval aviators.

Captain William Merrill Silliphant, (M.C.), U. S. N., F.A.C.P., has recently been appointed Deputy Director, Armed Forces Institute of Pathology, Washington, D. C. He was formerly Director of Laboratories, U. S. Naval Medical School, Bethesda, Md.

Dr. Alfred C. LaBoccetta, F.A.C.P., Chief of the Hospital for Contagious Diseases, Philadelphia, has been appointed acting Director of Philadelphia General Hospital. He will also hold the position of Chief of the Bureau of Hospitals and will continue as Chief at the Hospital for Contagious Diseases.

Dr. John William Roy Norton, F.A.C.P., has been appointed by Dr. Leonard A. Scheele, F.A.C.P., Surgeon General, a Trade Association Liaison Representative to the Division of Civilian Health Requirements, U. S. Public Health Service. As State Health Officer of the N. C. State Board of Health, Raleigh, N. C., he represents the Association of State and Territorial Health Officers.

At the 160th Annual Meeting of the Connecticut State Medical Society held on April 29–May 1, 1952, Dr. Robert L. Levy, F.A.C.P., Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, talked on "Coronary Heart Disease as a Problem in General Practice." He also joined Dr. John G. Mateer, F.A.C.P., in a "Symposium on Indispensable Therapeutics."

Dr. William T. Salter, F.A.C.P., representing the Yale School of Medicine, and Dr. Hugh L. Dwyer (Associate), representing the Connecticut State Medical Society, have recently been appointed to the Connecticut Committee on Foods, Drugs, Cosmetics and Devices.

Dr. Konrad Birkhaug, F.A.C.P., was a principal speaker at the Annual New Haven County Medical Association Meeting held March 27 in New Haven, Conn. His topic was "The World Health Organization's International Crusade Against Tuberculosis."

Dr. Norman M. Shure (Associate), of Los Angeles, Calif., was recently elected President of the Los Angeles Society of Allergy.

Dr. M. William Barry, F.A.C.P., Associate Professor of Medicine, was one of three Omaha physicians on the faculty of Creighton University School of Medicine who received plaques in recognition of 25 years of service at a Founders Day dinner in December.

Dr. Emanuel B. Schoenbach, New York, Professor of Medicine at the University of New York Medical Center at Brooklyn and Director of Medical Services at Maimonides Hospital, Brooklyn, has succeeded Dr. Paul W. Clough, F.A.C.P., of Baltimore as Editor-in-Chief of the *Quarterly Review of Internal Medicine and Dermatology*. Dr. Schoenbach has been on the faculty of the Johns Hopkins University School of Medicine, and is a member of the Committee on Cancer Diagnosis and Therapy of the National Research Council, as well as a consultant to the National Cancer Institute.

Dr. Clough, who has been associated with the Johns Hopkins University School of Medicine since his graduation from that institution in 1907, is also the Assistant Editor of the ANNALS OF INTERNAL MEDICINE.

Dr. Esmond Long, F.A.C.P., of Philadelphia, has recently resigned as Executive Secretary of the American Trudeau Society, which position he has held since 1947, in order to devote more time to the National Tuberculosis Association's expanding program of medical research. As of December 31, 1951, Dr. Long also resigned as Editor-in-Chief of the *American Review of Tuberculosis*, but will continue as consulting editor. He is also Director of the Henry Phipps Institute of the University of Pennsylvania.

Dr. Francis J. Braceland, F.A.C.P., newly appointed Psychiatrist-in-Chief at the Institute of Living, Hartford, Conn., was guest of honor at a dinner held January 31 by the Directors of the Institute. More than 350 Connecticut physicians attended the dinner, and among the country's outstanding psychiatrists were: Dr. S. Bernard Wortis, F.A.C.P., of New York City, President of the American Neurological Association; Dr. Daniel Blain, F.A.C.P., of Washington, D. C., Medical Director of the American Psychiatric Association; Dr. Leo Bartemeier of Detroit, President of the American Psychiatric Association; and Dr. Houston Merritt of New York City, President of the Association for Research in Nervous and Mental Diseases. Dr. Thomas P. Murdock, F.A.C.P., A.C.P. Governor for Connecticut, was one of the speakers who paid tribute to Dr. Braceland, emphasizing the fitting qualities which he possesses for his new position.

At the annual meeting of the Florida Medical Association, held April 28–30 in Tampa, Fla., Dr. Steven O. Schwartz, F.A.C.P., Chicago, acted as moderator for a symposium on hypersplenism.

Dr. Wallace M. Yater, F.A.C.P., was the moderator of a panel on "The Need for Teaching the Teachers," which was part of the program of a Conference of Medical Teaching Techniques, sponsored by the Medical Society of the District of Columbia on April 4–5. Members of other panels at the same conference included Dr. Walter C. Alvarez, F.A.C.P., Chicago, and Dr. Hugh H. Hussey, F.A.C.P.

At the Annual Missouri State Medical Society Meeting held in St. Louis, March 31–April 2, Dr. Walter C. Alvarez, F.A.C.P., spoke on the topic, "Why Some People Are So Terribly Nervous"; and Dr. Hans Popper, F.A.C.P., spoke on "Hepatitis: Differential Diagnosis by Laboratory Studies." Dr. Louis H. Bauer, F.A.C.P., President-Elect of the American Medical Association, addressed the closing banquet on "Problems Facing the Medical Profession."

Among the guest lecturers at the Second Annual Institute in Psychiatry and Neurology, held at the Veterans Administration Hospital, Lyons, N. J., on April 16

were: Dr. Harvey J. Tompkins, F.A.C.P., Chief, Psychiatry and Neurology Division, Veterans Administration; Dr. Daniel Blain, F.A.C.P., Medical Director, American Psychiatric Association; and Dr. Edward G. Billings, F.A.C.P., Associate Clinical Professor of Psychiatry, University of Colorado School of Medicine, Denver.

Dr. Edgar V. Allen, F.A.C.P., of Rochester, Minn., addressed the Iowa State Medical Society at its Annual Meeting in Des Moines, April 27–30, on the topic, "What Can Be Done About Hypertension?"

Dr. John E. Gordon, F.A.C.P., Professor of Epidemiology, Harvard University School of Public Health, Boston, Mass., is a member of the World Health Organization Medical Team for Southeast Asia, which is currently studying medical problems in Calcutta, Rangoon and Colombo.

Dr. Harold Trimble, F.A.C.P., of Oakland, Calif., Consultant, Diseases of the Chest, Alameda County Institutions, addressed the recent conference on "Modern Concepts of Tuberculosis for Nurses and Allied Medical Services" in Sacramento. His topic was "Epidemiology of Tuberculosis."

Dr. Marcos Fernan-Nunez, F.A.C.P., Chief Pathologist and Director of Laboratories at the Dublin Veterans Administration Hospital, Dublin, Ga., has recently been advanced to the grade of Chief, the highest rating in the Veterans Administration Department of Medicine and Surgery.

Dr. Claude Forkner of New York City, who has been medical adviser to Chiang Kai-shek and the Shah of Iran, was the chief speaker at the Annual Dinner of the American Heart Association at Cleveland, April 18, his topic being "Iran Is Ill—A Physician's Consultation."

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., was recently elected to membership in The Scientific Research Society of America and the American Association for the Advancement of Science.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was a delegate to the Third Pan-American Working Day of Gastro-enterology held in Mexico City, May 11–17, 1952, and to the Third European Congress of National Societies of Gastroenterology held in Bologna, Italy, April 20–26, 1952.

Roscoe L. Pullen, M.D., F.A.C.P., heretofore Director of the Division of Graduate Medicine and Vice Dean of the Tulane University of Louisiana School of Medicine, New Orleans, has resigned to become Dean and Professor of Medicine at the University of Texas Postgraduate School of Medicine in Houston, effective June 1, 1952.

Dr. E. Rankin Denny, F.A.C.P., formerly Medical Consultant and Director of the Clinical Laboratory, Daviess County Hospital, Washington, Ind., is now a member of the Medical Center Clinic, 5th and Cherokee Sts., Bartlesville, Okla.

Dr. Robert R. Commons (Associate) was elected Chairman of the Western Section of the American Federation of Clinical Research at the annual meeting at Carmel,

Calif., last January. Dr. Commons is Assistant Clinical Professor of Medicine at the University of Southern California School of Medicine, Los Angeles.

Dr. Hans H. Reese, F.A.C.P., Professor of Neurology and Psychiatry at the University of Wisconsin Medical School, has been appointed Chairman of the Medical Advisory Board of the National Multiple Sclerosis Society for a two-year term.

William C. Moloney, M.D., F.A.C.P., Clinical Professor of Medicine, Tufts Medical School, and Assistant Director of the First and Third (Tufts) Medical Services, at the Boston City Hospital, will serve in Japan for the next two years as internist with field units of the Atomic Bomb Casualty Commission which are engaged in the study of the effects of atomic radiation in Hiroshima and Nagasaki. This work is under the direction of the National Research Council and the National Academy of Science.

Elections to Membership in The American College of Physicians

At the Thirty-third Annual Session held in Cleveland, Ohio, April 21–25, the following candidates were elected to membership in the College. FELLOWS APPEAR IN FULL CAPITALS; Associates, lower case.

Albert Abraham.....Morristown, N. J.
ESTA ROSS ALLEN.....Clarksburg, W. Va.
HOWARD EDWIN ALLEN.....Portland, Ore.
ROBIN NAIL ALLIN, SR.....Madison, Wis.
William Lewis Alsobrook.....Nashville, Tenn. (V.A.)
William Howard Ames.....Iowa City, Iowa
Vito Charles Ancona.....Bronxville, N. Y.
LEIGHTON LARS ANDERSON.....Denver, Colo.
Milton Winfield Anderson.....Rochester, Minn.
MAURICE JOSEPH ANSFIELD.....Milwaukee, Wis.
Robert John Anzinger.....Cincinnati, Ohio
Hugh Fuller Arnold.....Houston, Tex.
Allan Russell Aronson.....New York, N. Y.
Daniel Benjamin Arst.....Newington, Conn. (V.A.)
Samuel Philips Asper, Jr.....Baltimore, Md.
*Levon Fred Ayvazian.....New York, N. Y.

Lesem James Baer.....Dearborn, Mich. (V.A.)
JAMES ADAM BARR.....Oakland, Calif.
Theodore Lawrence Bartelmez.....M.C., U. S. Army
ALEXANDER GEORGE BARTLETT.....San Francisco, Calif.
Robert Richard Bartunek.....Cleveland, Ohio
Owen Wayne Beard.....Little Rock, Ark.
Charles Samuel Becker.....Cleveland, Ohio
Marvin Caesar Becker.....Newark, N. J.
HERBERT BERGER.....Staten Island, N. Y.
JOHN WILLIAM BERRY.....Denver, Colo.
John Gordon Bielawski.....Detroit, Mich.
HOWARD RICHARD BIERMAN.....San Francisco, Calif.
John Hardesty Bland.....Burlington, Vt.
A(DOLPH) EBNER BLATT.....Indianapolis, Ind.

* (MC), AUS.

Lewis William Bluemle, Jr. ..... Philadelphia, Pa.
JOHN LYNCH BOHAN ..... Galesburg, Ill.
George Moore Boyden ..... Toledo, Ohio
FREDERICK JOSEPH BRADSHAW, JR. ... Fort Meade, S. D. (V.A.)
William Edward Bray, Jr. ..... Huntington, W. Va.
Theodore Tobias Bronk ..... Buffalo, N. Y.
NORRIS L. BROOKENS ..... Urbana, Ill.
CHARLES HOWARD BROWN ..... Cleveland, Ohio
EARL BENEDICT BROWN, SR. ..... New York, N. Y.
GEORGE EMERSON BROWN, JR. ..... Twin Falls, Idaho
Randolph Kelley Brown ..... Washington, D. C.
ROBERT HAMILTON BROWNING ..... Columbus, Ohio
Maurice Madison Burkholder ..... Boise, Idaho
John Joseph Butler ..... Wooster, Ohio
George Velmer Byfield ..... Chicago, Ill.

HERBERT RICHARD CAMMERER ..... Dayton, Ohio
James William Campbell ..... Lawrence, Kans.
ORLANDO CANIZARES ..... New York, N. Y.
DAVID TURNER CARR ..... Rochester, Minn.
EDWARD MILTON CHESTER ..... Berea, Ohio
James Logan Chitwood ..... Pulaski, Va.
John James Christian ..... Temple, Tex.
ELMER FREDOLPH CHRISTOPHERSON .. Vancouver, B. C., Can.
Muir Clapper ..... Detroit, Mich.
John Kapp Clark ..... Philadelphia, Pa.
Roger Gold Clarke ..... Quincy, Ill.
ARCHIBALD CLINTON COHEN ..... Butler, Pa. (V.A.)
Andrew William Contratto ..... Brookline, Mass.
WILLIAM LEIGH COOK, JR. ..... Pittsburgh, Pa.
Eliot Corday ..... Los Angeles, Calif.
Nila Kirkpatrick Covalt ..... East Hampton, Conn.
Wallis Landes Craddock ..... Jefferson Barracks, Mo. (V.A.)
Girard Joseph Craft ..... Hudson, N. Y.
ROBERT CLIFFORD CRAWFORD ..... Roanoke, Va.
Richard Irving Crone ..... M.C., U. S. Army
GARY ARNOLD CRONK ..... Syracuse, N. Y.
HAROLD ROLAND CUMMINGS ..... Los Angeles, Calif.
Edward Patrick Cummins ..... Cortland, N. Y.
DONAT PAUL CYR ..... Boston, Mass.

Oscar Theodore Davis ..... Owensboro, Ky.
EDWARD DOANE DELAMATER ..... Philadelphia, Pa.
Victor George deWolfe ..... Cleveland, Ohio
Morris William Dexter ..... Cincinnati, Ohio
ROBERT DICKES ..... Brooklyn, N. Y.
Lewis Dickinson ..... Glasgow, Ky.
Thomas Gerard Dineen ..... Lansdowne, Pa.
ARTHUR LEO DONOVAN ..... St. John, N. B., Can.
TRUMAN GUTHRED DRAKE, JR. ..... St. Louis, Mo.

JOHN NEWELL EDSON ..... Brooklyn, N. Y.
Laszlo Ehrlich ..... San Juan, P. R. (V.A.)

Lee Ehrlich.....Phoenix, Ariz.
Herman Levy Eisenberg.....Chicago, Ill.
Samuel Leon Elfmon.....Fayetteville, N. C.
Michael Edward Ellis.....Grand Rapids, Mich.
Harold Martin Engle.....Spokane, Wash. (V.A.)
William George Ensign.....Minot, N. D.
ALBERT JOHN ERDMANN, JR.....New York, N. Y.
*Solomon Estren.....New York, N. Y.
Ernest Joseph Eytinge.....Everett, Wash.

Seymour Albert Fink.....New York, N. Y.
Martin Milton Fisher.....Brooklyn, N. Y.
Joseph Michael Fitzgerald.....New York, N. Y.
WILLIAM HENRY FLYTHE.....High Point, N. C.
David Hudson Fogel.....Stamford, Conn.
MORRIS FOGEL.....Brooklyn, N. Y.
John Albert Fownes.....Moncton, N. B., Can.
Robert Edward Fox.....St. Louis, Mo.
MAX S(CHWAB) FRANKLIN.....St. Louis, Mo.
Robert Blair Franklin.....M.C., U. S. Army
ARTHUR FREEDMAN.....Greensboro, N. C.
RUDOLPH ERIC FREMONT.....Albany, N. Y. (V.A.)
ROBERT FRIEDENBERG.....Albuquerque, N. M.
CARL KAMPTON FRIEDLAND.....Philadelphia, Pa.
JOSEPH DAVID FRIEDLAND.....Denver, Colo.
Abraham Maurice Frumin.....Philadelphia, Pa.
WILLIAM WESLEY FRYE.....New Orleans, La.

RAYMOND MASSON GALT.....Chicago, Ill.
ROBERT ODELL GARVIN.....Pittsburgh, Pa.
Leo S. Gelfand.....Los Angeles, Calif.
Aaron Philip Gewanter.....Somerville, N. J.
Joseph Edward Giansiracusa.....San Francisco, Calif.
HORACE CRAIG GIBSON.....M.C., U. S. Army
Carl Norman Giere.....Sacramento, Calif.
David Givner.....Indianapolis, Ind.
George B. Jerzy Glass.....New York, N. Y.
HERMAN GOLD.....Chester, Pa.
MORRIS ALAN GOLD.....Butte, Mont.
MERVIN JACK GOLDMAN.....Oakland, Calif. (V.A.)
JOSEPH IRVING GOODMAN.....Shaker Heights, Ohio
Rowland Davies Goodman, 2nd.....East Orange, N. J.
ROBERT ARCHER GOODWIN, JR.....Nashville, Tenn. (V.A.)
JOHN RUSKIN GRAHAM.....Boston, Mass.
Monroe Henry Green.....Phoenix, Ariz.
Henry McClellan Greenleaf.....M.C., U. S. Army
GERARD PATRICK JOSEPH GRIFFIN.....Brooklyn, N. Y.
Dwight Griswold.....Hartford, Conn.
Harry Arnold Grubschmidt.....Santa Rosa, Calif.
Marshall Beck Guthrie.....M.C., U. S. Army

William Thomas Hall.....White Sulphur Springs, W. Va.
John Dallas Hallahan.....Media, Pa.

* (MC), AUS.

Shea Halle.....New Orleans, La.
Franklin Foster Ham.....Van Nuys, Calif.
Stanley Forrest Hampton.....St. Louis, Mo.
George John Hamwi.....Columbus, Ohio
B(ENJAMIN) MARVIN HAND.....Philadelphia, Pa.
Robert Harold Hansen.....Dearborn, Mich. (V.A.)
Komuria Albert Harden.....Washington, D. C.
J(OHN) THOMAS HARDESTY.....Long Beach, Calif.
ROBERT CALVIN HARDIN.....Iowa City, Iowa
FRANCIS NELSON HATCH.....Modesto, Calif.
Edward Wray Hauch.....Rochester, Minn.
WELLAND ANGEL HAUSE.....Decatur, Ill.
Frederick Mullen Hebert.....Berkeley, Calif.
James Spencer Hewlett.....Lexington, Ky.
RALPH EMERSON HIBBS.....Medford, Ore.
Daniel Joseph Hilferty, Jr.....Swarthmore, Pa.
ALFRED HUMPHREY HILL.....San Antonio, Tex.
William Armitage Hines.....Denver, Colo.
J(ohn) G(eorge) Fred Hiss.....Syracuse, N. Y.
Paul Ingalls Hoagland.....Pasadena, Calif.
Robert John Hoagland.....M.C., U. S. Army
Harry Teel Hoffman.....Easton, Pa.
DANIEL HOLZMAN.....Brookline, Mass. (V.A.)
David Case Humphrey.....Cleveland, Ohio
PATRICK CONNELL HUMPHREYS.....Los Angeles, Calif.
Frank Edward Hurley.....Springfield, Mass.
LEROY HYDE.....Long Beach, Calif. (V.A.)

Stanford Irving Isaacson.....Pittsburgh, Pa.
LOUIS ARTHUR IZENSTEIN.....Springfield, Mass.

Daniel Jackson.....Houston, Tex.
Thomas Price Jacobs.....New Rochelle, N. Y.
Thomas Jarrold.....Dayton, Ohio (V.A.)
William Jend, Jr.....Dearborn, Mich. (V.A.)
LELAND MANN JOHNSTON.....Jackson, Tenn.
REVERDY HAMLIN JONES, JR.....Roanoke, Va.
William Edgar Jones.....Texarkana, Tex.

JULIUS KAHN.....Beverley Hills, Calif.
NOLAN LEVI KALTREIDER.....Rochester, N. Y.
Rubin Harry Kaplan.....Oteen, N. C. (V.A.)
David Kastoff.....New York, N. Y.
Hilliard Joel Katz.....San Francisco, Calif.
EMMETT LEROY KEHOE.....M.C., U. S. Army
WALTER KEMPNER.....Durham, N. C.
RICHARD NELSON KENT.....Fort Wayne, Ind.
W(INFRED) PRICE KILLINGSWORTH.....Port Arthur, Tex.
HARRY EDWARD KING.....Dayton, Ohio
Eugene Clifford Klein.....New York, N. Y.
Leslie Charles Koch.....Rocky Mount, N. C.
LAWRENCE MELVIN KOTNER.....St. Louis, Mo.
David I. Kraft.....New York, N. Y.
Seymoure Krause.....Braddock, Pa.

Bernard Leo Kreilkamp.....Twin Falls, Idaho
Philip Louis Kurtz.....Indianapolis, Ind.
JOSEPH FRANCIS KUZMA.....Wauwatosa, Wis.

ROBERT LACHANCE.....Verdun, Que., Can.
William Bain Leffler.....Marion, Ohio
Samuel Richardson Lehrman.....Cedarhurst, N. Y.
MAURICE EMANUEL LEONARD.....San Francisco, Calif.
C(LARENCE) RALPH LETTEER.....San Antonio, Tex.
*Bertram Leonard Levy.....Mountain Home, Tenn. (V.A.)
BERNARD IRVIN LEWIS.....Iowa City, Iowa
Irving Maxwell Liebow.....Cleveland, Ohio
DAVID LITTMANN.....Belmont, Mass. (V.A.)
LENIER ARTHUR LODMELL.....Portland, Ore.
Arch Hodge Logan, Jr.....Spokane, Wash.
Stanley Herman Lorber.....Philadelphia, Pa.
Charles Rodney Lowe.....Casper, Wyo.
HOPE LOWRY.....Denver, Colo.
HAROLD DUFF LYNCH.....Evansville, Ind.

Peter Paul Machung.....M.C., U. S. Navy
HAROLD JOSEPH MAGNUSON.....Chapel Hill, N. C. (U.S.P.H.S.)
Clayton Hunter Manry.....Alton, Ill.
BENJAMIN FRANKLIN MARTIN.....Winston-Salem, N. C.
ELWOOD WHITTIER MASON.....Milwaukee, Wis.
Robert Lee Mayock.....Philadelphia, Pa.
James Lester McCallum.....Montreal, Que., Can.
JAMES MARSHALL McFADDEN.....La Fayette, Ind.
Theresa McGovern.....New York, N. Y.
James Reeder McMillan.....New York, N. Y.
Thomas S. G. McMurtry.....Vernon, B. C., Can.
DONALD LAUCHLIN McNEIL.....Calgary, Alta., Can.
MANSON MEADS.....Winston-Salem, N. C.
Jacob Meislin.....Montrose, N. Y. (V.A.)
JOHN KIMBERLY MENEELY, JR.....Albany, N. Y.
Henry Clarkson Meredith, Jr.....Norfolk, Va.
Harold Maurice Messenger.....San Diego, Calif.
LAWRENCE MEYERS.....New York, N. Y.
Muriel Charlotte Meyers.....Ann Arbor, Mich.
C(HARLES) JOSEPH MILLER.....Philadelphia, Pa.
Franklin Rush Miller.....Philadelphia, Pa.
JAMES REX MILLER, JR.....Salt Lake City, Utah
Jay Wolfe Miller.....New York, N. Y.
SAMUEL IRVING MILLER.....Houston, Tex.
WILLIAM BENDER MILLER.....Harrisburg, Pa.
Duane Herbert Mitchel.....Denver, Colo.
James Joseph Moher.....Hartford, Conn.
JAMES MONROE.....Ray Brook, N. Y.
Lee Monroe.....San Diego, Calif.
MAURICE ROBERTS MOORE.....Norwich, Conn.
FRANKLIN BERNARD MOOSNICK.....Lexington, Ky.
Laurence Andrew Mori.....Providence, R. I.
JACOB COPPLE MOSCOVICH.....West Vancouver, B. C., Can.

* (MC), AUS.

Campbell Moses, Jr.....Pittsburgh, Pa.
ELI RODIN MOVITT.....Oakland, Calif. (V.A.)
EARL I. MULMED.....Tulsa, Okla.

James Carroll Nash.....Huntsville, Ala.
Edward Gregory Nedwicki.....Detroit, Mich.
JOSEPH BRITTON NEIGHBORS, JR.....Athens, Ga.
RUSSELL ANDREW NELSON.....Baltimore, Md.
Harold Lawrence Neuenschwander.....Knoxville, Tenn.
William Neil New.....M.C., U. S. Navy
DAVID NIEMETZ.....Beverly Hills, Calif.
Joseph William Noah.....Webster Groves, Mo.
JACKSON NORWOOD.....Pasadena, Calif.
BERNARD EMILIO NUNEZ.....Washington, D. C.

Robert Loring Ohler.....Togus, Maine (V.A.)
ELLIOT OPPENHEIM.....Scarsdale, N. Y.
Edwin Marvin Ory.....Houston, Tex.
WILLIAM FRAZIER OWEN, JR.....Santa Ana, Calif.

FRANKLIN KITTREDGE PADDOCK.....Pittsfield, Mass.
EDDY DAVIS PALMER.....M.C., U. S. Army
A(RTHUR) SEYMOUR PARKER, JR.....Boston, Mass.
CLARENCE COPLYN PEARSON.....Seattle, Wash.
George Arthur Peck.....Salt Lake City, Utah
MARTIN PERLMUTTER.....Brooklyn, N. Y.
Edward Louis Perry.....La Crosse, Wis.
JOHN JOSEPH PHAIR.....Cincinnati, Ohio
RICHARD FRANCE PLATZER.....Clifton Springs, N. Y.
Joseph Neilson Plumer.....Tucson, Ariz. (V.A.)
HERBERT WILLIAM POHLE.....Milwaukee, Wis.
Harvey Poliakoff.....Rockville Centre, N. Y.
BYRON EDWARD POLLOCK.....M.C., U. S. Army
Simour David Pomrinse.....Springfield, Ohio
George Vernon Potter.....M.C., U. S. Army
William Arthur Pratt.....Rutland, Vt.
Claude Townsend Prevost.....Anderson, S. C.
JOSEPH DIXON PURVIS, JR.....Butler, Pa.
Willard Pushkin.....Charleston, W. Va.

E(DWIN) DANFORD QUICK.....Riverside, Calif.

LOWELL ADDISON RANTZ.....San Francisco, Calif.
EMANUEL MORTIMER RAPPAPORT.....Jamaica, N. Y.
Edwin Albert Rasberry, Jr.....Wilson, N. C.
Harold Elton Ratcliffe.....M.C., U. S. Army
James Clark Reavis.....San Leandro, Calif.
William Francis Renner.....Baltimore, Md.
Jerome Ritter.....Lincoln, Nebr.
Manuel Rodstein.....New York, N. Y.
Thomas Perrette Rogers.....M.C., U. S. Navy
Morton Harold Rose.....Washington, D. C.
Melvin David Roseman.....Boston, Mass.
Edgar Rosen.....Oakland, Calif. (V.A.)
Morris Hirsh Rosenberg.....Washington, D. C.

Sidney Rosenfeld.....New York, N. Y.
JOHN RICHARD ROSS.....Milton, Mass.

MAURICE SEVILLE SACKEY.....Philadelphia, Pa.
LOUIS MICHAEL SALES.....Jacksonville, Fla.
Max Samter.....Oak Park, Ill.
Samuel Hope Sandifer.....M.C., U. S. Army
Richard Henry Saunders, Jr.....Burlington, Vt.
James Adam Schaal.....Cincinnati, Ohio
Samuel Ely Schechter.....St. Louis, Mo.
ROBERT EMMETT SCHERB.....Bakersfield, Calif.
Fred Joseph Schilling.....New York, N. Y.
ISADORE SCHLAMOWITZ.....New York, N. Y.
Harry Morton Schneider.....Jersey City, N. J.
ROBERT WOODROW SCHNEIDER.....Cleveland, Ohio
EDWARD DAVID SCHWARTZ.....Cleveland, Ohio
I. RICHARD SCHWARTZ.....Brooklyn, N. Y.
SAMUEL HAROLD SCHWARTZ.....Plainfield, N. J.
ADDISON BEECHER SCOVILLE, JR.....Nashville, Tenn.
JOHN RIDLEY SEAL.....M.C., U. S. Navy
Paul Minor Seebohm.....Iowa City, Iowa
JUNE CAROL SHAFER.....Arlington, Va.
Lorne Shapiro.....Montreal, Que., Can.
Ernest W. Shaw.....San Diego, Calif.
Hyman Rock Sheintoch.....Brooklyn, N. Y.
Edward Paul Sheridan.....Denver, Colo.
Roger Davis Sherman.....M.C., U. S. Navy
EMANUEL SIGOLOFF.....Los Angeles, Calif. (V.A.)
AARON SILVER.....New York, N. Y.
Albert Myron Silver.....Newark, N. J.
EUGENE EARL SIMMONS.....Omaha, Nebr.
ETHAN ALLEN HITCHCOCK SIMS.....South Burlington, Vt.
Richard Hopkins Sinden.....St. Petersburg, Fla.
Joseph Skwirsky.....Newark, N. J.
MAURICE JACOB SMALL.....Staten Island, N. Y. (V.A.)
Jackson Algernon Smith.....Houston, Tex.
Walter Spaeth.....Elizabeth City, N. C.
PAUL WILLIAM SPEAR.....Flushing, N. Y. (V.A.)
HELMUTH SPRINZ.....M.C., U. S. Army
Maxwell Wensel Steel, Jr.....M.C., U. S. Air Force
TOBIAS STEIN.....Montgomery, Ala. (V.A.)
Charles A. L. Stephens, Jr.....Tucson, Ariz.
John Edgar Stevens.....Richmond, Va.
Samuel Lewis Swiller.....Brooklyn, N. Y.
John Louis Switzer.....Chicago, Ill.

THEODORE JOSEPH TALBOT.....Staten Island, N. Y.
Robert D. C. Tarpey.....New York, N. Y.
SOLOMON TAUBIN.....Yonkers, N. Y.
Alfred Melville Taylor.....Crossville, Tenn.
Charles Edward Test.....Indianapolis, Ind.
STEPHEN BENEDICT THORSON.....Calgary, Alta., Can.
WILLIAM JOSEPH TIGHE.....San Diego, Calif.
Lloyd Flintom Timberlake.....Atlanta, Ga.

E. PAUL TISCHER.....Indianapolis, Ind.
CHARLES ROBERT TITTLE, JR.....Glenside, Pa.
Robert Bruce Tudor.....Bismarck, N. D.

Laurentius Olaves Underdahl.....Rochester, Minn.

Luis Enrique Viteri.....Mount Holly, N. J.
ODON FRANCIS VON WERSSOWETZ.....Nashville, Tenn. (V.A.)
ARTHUR JOHN VORWALD.....Saranac Lake, N. Y.
Glenn Quintin Voyles.....Twin Falls, Idaho

EPHRAIM LIONEL WAGNER.....Houston, Tex.
Richard Parish Walker.....Memphis, Tenn.
Lester Aubrey Wall, Jr.....Baltimore, Md.
Robert Wallach.....New York, N. Y.
DAVID MICHAEL WAYNE.....Fort Meade, S. D. (V.A.)
FREDERICK CLARENCE WEBER, JR.....Greenwich, Conn.
Irving Wecksell.....Maspeth, N. Y.
John Harrison Wedig.....Alton, Ill.
Paul John Weigel.....Buffalo, N. Y.
HARRY BERNARD WEINBERG.....Davenport, Iowa
TOBIAS WEINBERG.....Baltimore, Md.
William Weingarten.....Staten Island, N. Y. (U.S.P.H.S.)
Arvin Bernard Weinstein.....Madison, Wis.
LOUIS WEINSTEIN.....Brookline, Mass.
BENJAMIN BAXTER WELLS.....Little Rock, Ark.
Edward Buist Wells.....Erie, Pa.
George Marshall Whitacre.....Bremerton, Wash.
Joseph Lawrence Whitaker.....Sherman Oaks, Calif.
Charles Allen White.....Cleveland, Ohio
Neil Kenneth White.....Menlo Park, Calif.
IRA WICKNER.....Wallkill, N. Y.
Nathan David Wilensky.....Brooklyn, N. Y.
HUGH LYON CLEMENTS WILKERSON..Needham, Mass. (U.S.P.H.S.)
JAMES MACLEAN WILKIE.....Madison, Wis.
Carl Daniel Winternitz.....San Francisco, Calif.
Thomas Adams Witten.....Fort Logan, Colo. (V.A.)
Stanley Jackson Wittenberg.....New York, N. Y.
A(RTEMUS) FORD WOLF.....Temple, Tex.
ROBERT WILLIAM WOLFORD.....Mansfield, Ohio
Charles Ray Womack.....Nashville, Tenn.
JAMES WATSON WOODS, JR.....Durham, N. C.
ROBERT MORGENTHALER WOOLFORD..Cincinnati, Ohio
Frank Mahlon Woolsey, Jr.....Albany, N. Y. (V.A.)

Harry Joseph Yellen.....Chicago, Ill.
Richard Philip Yoder.....Bluffton, Ind.

Manuel David Zane.....New York, N. Y.
CHRIS JOHN DIMITER ZARAFONETIS...Philadelphia, Pa.
Jacob Zatuchni.....Philadelphia, Pa.
WALTER JACOB ZEITER.....Cleveland, Ohio
LYNWOOD DUANE ZINN.....Clarksburg, W. Va.
Simon Zivin.....Chicago, Ill.
Hyman Zuckerman.....New York, N. Y.
Herman Bernard Zurrow.....New York, N. Y.

OBITUARIES

DR. CHARLES D. AARON

Charles D. Aaron, M.D., F.C.D., F.A.C.P., Physician and Professor Emeritus of Gastro-enterology and Dietetics at Wayne University College of Medicine, Detroit, Mich., died December 3, 1951.

Dr. Aaron was born May 8, 1866, in Lockport, New York. He attended the University of Syracuse two years and received his M.D. degree from the University of Buffalo in 1891. After postgraduate work in Vienna, Paris and London, he entered private practice in the City of Detroit. In 1905 he became Professor of Gastro-enterology and Dietetics at the Wayne University College of Medicine, in which capacity he continued to serve until 1938 when he was appointed Emeritus. He was also consulting gastro-enterologist to Harper Hospital, the Tuberculosis Hospital, Shurly Hospital and the Receiving Hospital in Detroit.

Dr. Aaron's bibliography was extensive. Among other publications, he was the author of "Diseases of Digestive Organs, with Special Reference to Treatment," which was first published in 1915 by Lea & Febiger and later had revised editions in 1916, 1921 and 1927. He was a member of many scientific organizations and became a Fellow of the American College of Physicians in 1916, and was a Regent of the College in 1922–23. He retired from active work on February 1, 1951.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

CAPTAIN GEORGE ALBERT ALDEN

Capt. George Albert Alden, (MC), USN, Retired, M.D., F.A.C.P., died at his home in Philadelphia, March 17, 1952. He was born in Leicester, Vermont, on September 5, 1891. He was graduated from the University of Vermont College of Medicine in 1917 and took postgraduate medical training at the Massachusetts General Hospital, the New York Graduate Hospital and the U. S. Naval Medical School.

A veteran of thirty-three years in the Navy until his retirement in 1950, he was commissioned a Lieutenant (junior grade) in the Medical Corps, U. S. Naval Reserve, on May 19, 1917, transferring to the regular Navy in 1918. Most of his World War I service was a medical officer aboard transports. Other sea duty included assignments abroad and aboard several ships of the Fleet, which included duties as senior medical officer aboard the *U. S. S. Houston*, which made the Presidential cruise to Galapagos Island with the late President Franklin D. Roosevelt.

Capt. Alden was stationed at the U. S. Naval Hospitals in New York City and Norfolk, Va., and at one time was instructor in anatomy, physiology, and therapeutics at the Pharmacist's School, Hampton Roads, Va.

From 1929–31 he was the Senior Medical Officer at the Guard Hospital in Port au Prince, Haiti. Capt. Alden later became head of the Department of Pathology and Hematology and Postgraduate Instructor at the U. S. Naval Medical School in Washington from July, 1931, to May, 1936. Following this tour of duty, he was Chief of Laboratories in the School for Laboratory Technicians at Norfolk, Va.

After World War II Capt. Alden was Executive Officer at the U. S. Naval Hospital, Portsmouth, Va., and Commanding Officer of the U. S. Naval Hospitals, Bainbridge, Md., and Portsmouth, N. H. He was later stationed in the Office of Naval Officer Procurement, Philadelphia, Pa.

Upon his retirement from the Navy he became Pathologist at the J. Lewis Crozer Homeopathic Hospital, Chester, Pa.

Capt. Alden was elected to Fellowship in the American College of Physicians in 1934 and was, in addition, a member of the American Medical Association, the American Association of the Study of Neoplastic Diseases, the Washington Society of Pathologists, British Medical Society, London, England, 1941–42, and was registered with the American Society of Clinical Pathologists.

DR. ROBERT ALFRED BLACK

Dr. Robert Alfred Black, F.A.C.P., died January 13, 1952, at the age of 72 in Maitland, Fla. Dr. Black was born in Clarksburg, Pa., in 1879, and spent most of his professional life in the Chicago area. He had moved to Florida in 1950 when he suffered a severe coronary attack.

Dr. Black's specialty was Pediatrics, and the success he achieved in his field is evidenced by the fact that he was Emeritus Professor and Head of the Department of Pediatrics at Loyola University School of Medicine, from which he himself had received his medical degree in 1904. In addition, Dr. Black was a Diplomate, American Board of Internal Medicine, a member of the American Academy of Pediatrics, and a past President of the Chicago Pediatric Society, and had been a Fellow of the American College of Physicians since 1919.

During late 1938 and early 1939 he served as President of the Chicago Board of Health, of which he was a member for many years. Dr. Black had also been Superintendent of the Jackson Park Sanitarium for Convalescent Cardiac Children and Attending Pediatrician at the Mercy Hospital as well as a member of the Advisory Board of the Municipal Contagious Disease Hospital of Chicago.

COLONEL ELIAS EARLE COOLEY

Colonel Elias Earle Cooley, (M.C.), U. S. A., Retired, A.B., M.D., F.A.C.P., was born in Hollands, Anderson County, S. C., on January 4, 1890, and died at his home in Greenville, S. C., on February 18, 1952.

He received his A.B. degree from Furman University and his M.D. from the Jefferson Medical College of Philadelphia, 1912. He interned at Gouverneur Hospital in New York, St. Lawrence Hospital, Ogdenburg, N. Y., and the Pennsylvania Hospital, Philadelphia.

During World War I, Col. Cooley was Assistant Surgeon with the American Ambulance Corps, Neuilly sur Seine, France. Col. Cooley entered the Army in March, 1917, and was later stationed at the Army General Hospital Number 43, Hampton, Va. From June, 1920, to January, 1925, he served as Ward Surgeon at the William Beaumont General Hospital in El Paso, Texas, and as Assistant to the Chief of Medical Service and later as chief of Medical Service at the Tripler General Hospital in Honolulu. From 1928 until 1934 Col. Cooley was Assistant Professor of Military Science and Tactics at Johns Hopkins University, and from 1931 until 1934 was also Assistant Dispensary Physician at the Johns Hopkins Hospital. For many years Col. Cooley served in the Professional Service Division of the Office of the Surgeon General until he was appointed Assistant Chief of the Medical Service, Letterman General Hospital, San Francisco, in October, 1938. He left this post in 1940 and was appointed Chief of Medical Service, Lawson General Hospital, Atlanta, Georgia, in 1941. During World War II Col. Cooley commanded the Twentieth General Hospital, which was stationed in the European Theatre of Operations. He retired from active duty in 1946.

Col. Cooley was a Fellow of the American Medical Association, became a Diplomate of the American Board of Internal Medicine in 1939 and a Fellow of the American College of Physicians in 1940. He also held memberships in the Greenville

County Medical Society, the South Carolina Medical Society, and the Association of Military Surgeons of the United States.

DR. WILLIAM GRIGSBY CRAWFORD

William Grigsby Crawford, M.D., F.A.C.P., was born at Putnamville, Indiana, January 24, 1883, and was the son of Leonard F. Crawford, a farmer, and Mrs. Eliza Grigsby Crawford. He was married to Lillian Brossman in 1919, to whom were born Frank and Jean. He was graduated from Greencastle High School and received his A.B. degree from DePauw University in 1905 and his M.D. degree from Indiana University School of Medicine in 1908. He located in Terre Haute, Indiana, June 16, 1908, and became a member of Vigo County Medical Society in 1908, and subsequently of Indiana State Medical Society and of American Medical Association. He was also a member of the Esculapian Society of Wabash Valley (1911) and the Terre Haute Academy of Medicine (1921). He entered the American College of Physicians as an Associate in 1924 and served as a Fellow from 1933. He was a Fellow of the American College of Chest Physicians and Indiana Trudeau Society. He was the physician for the Vigo County Tuberculosis Association for the past fifteen years. His postgraduate studies included a course at Harvard Medical School in 1916 in physical diagnosis and six weeks in tuberculosis at Trudeau Sanatorium in 1935. Dr. Crawford limited his practice to internal medicine since 1919. He belonged to the local clubs and took an active part in church work and politics.

In his later years, he was considered a senior medical consultant and especially so in the case of illness in a doctor's family. Quiet by nature, unruffled, and slow and deliberate in habit, he had the faculty of inspiring confidence. Ill health forced his retirement in 1948. On November 5, 1951, while in the terminal stage of Parkinson's disease, he died suddenly of arteriosclerotic heart disease in Wesley Memorial Hospital of Chicago.

Dr. Crawford will long be remembered by his associates for the fine gentleman and doctor that he was.

James O. Ritchey, M.D., F.A.C.P.,
Governor for Indiana

DR. JOHN RALEIGH DIBRELL

Dr. John Raleigh Dibrell, born in Little Rock, Arkansas, in 1877, died February 25, 1952, at the age of 74, in a Little Rock hospital, after a long illness, having retired from practice a few years ago. His passing brought to a close one of the most distinguished medical careers in the history of Arkansas for the Dibrell family. His grandfather, father, one brother and two uncles who preceded him in death, all were distinguished men in the profession.

Dr. Dibrell was an early graduate of the University of Arkansas School of Medicine, and later studied in New York. At one time he was assigned to a position with Thomas A. Edison in his New Jersey laboratories, in which he participated in some early experiments with x-rays, which resulted in severe x-ray burns of his hands. As professor of bacteriology and pathology at his alma mater in the early years of his practice, he was a prominent figure in the field of scientific research, particularly in the study and control of malaria.

Dr. Dibrell was associated with many of the activities of organized medicine throughout his career, and was noted for his helpful attitude in giving counsel to his younger colleagues. For many years he was chief of staff of St. Vincent's Hospital in Little Rock, a leader in his county and state medical societies, a Fellow of the American College of Physicians since 1928, and Diplomate of the American Board of Internal Medicine.

Many honors came to Dr. Dibrell in the course of his long and active career, but the greatest of these perhaps was the great affection and abiding respect of thousands of his former patients who mourn his demise.

A. A. Blair, M.D.,
Governor for Arkansas

DR. ALBERT H. DOLLEAR

Albert H. Dollear, M.D., F.A.C.P., was born November 3, 1876, at Jacksonville, Ill., and died October 30, 1951, at Jacksonville. He received his B.S. degree from Illinois College in 1901 (Phi Beta Kappa), and his M.D. degree from St. Louis University in 1904. On June 19, 1907, he was married to Pearl A. Gilbert, who preceded him in death February 19, 1947. Surviving are two sons, Dr. Henry A. Dollear, a physician on the staff of the Norbury Sanatorium, and Frank G. Dollear, a research chemist with the Department of Agriculture.

Dr. Dollear served his internship and residency at the Norbury Sanatorium (Jacksonville) from 1904 to 1906. He was in the state service from 1906 to 1912, serving at Watertown State Hospital, Illinois State Hospital, and Illinois State Psychopathic Institute at Kankakee. From 1912 to 1913 he was clinical assistant in neurology at Rush Medical College. From 1913 to the time of his death, he was Superintendent of the Norbury Sanatorium at Jacksonville, Ill. Dr. Dollear was a Fellow of the American College of Physicians (1920), a Fellow of the American Psychiatric Association, a member of the Mississippi Valley Medical Society, as well as of national, state and local medical societies. In addition to carrying a heavy professional load, Dr. Dollear was quite active in civic affairs, as is indicated by the fact that he was a director of the Illinois State Chamber of Commerce, past trustee of MacMurray College for Women, and District Governor of Rotary International. Dr. Dollear was highly respected as a consultant in psychiatry by numerous physicians in this district. His many friends and patients will miss him greatly.

Charles H. Drenckhahn, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. THOMAS N. HORAN

Thomas Neil Horan, A.B., M.D., F.A.C.P., of Detroit, Michigan, died suddenly at his home on December 1, 1951, following a coronary thrombosis. Dr. Horan was born in Detroit on April 3, 1902. After undergraduate work at the University of Michigan, he continued at that Medical School and graduated in 1926. For two years he taught in the Department of Anatomy.

Dr. Horan returned to Detroit for medical training at Harper Hospital and remained on this Staff throughout his medical years, attaining the position of Physician in 1943. In 1937 he became instructor at Wayne University College of Medicine and Assistant Professor of Clinical Medicine in 1946. He held attending consultant rank at the Dearborn Veterans Hospital and at Herman Keifer Hospital. He was a member of the Detroit Academy of Medicine, the Wayne County Medical Society, and the Detroit Medical Club. His Fellowship in the American College of Physicians dated back to 1938.

The major interest to which Dr. Horan was devoted was the private practice of internal medicine. He gave of himself untiringly to his devoted patients. He regarded himself as a family physician and was as much a friend as a doctor to the many who sought his advice.

Early in his medical career he became intrigued by the work of Jacobeus in the performance of peritoneoscopy. He perfected himself in this procedure at clinics which included the Wayne County General Hospital. From this work and his unusual

photographic ability, he developed an exhibit on laparoscopy and intra-abdominal photography in color which won honorable mention at the 1942 Session of the American Medical Association.

During World War II, he served with the 17th General Hospital (Harper) and was discharged from the Army as a Lieutenant Colonel. The epidemic of hepatitis in Italy engaged his attention and many peritoneoscopies were performed and extensive studies of the liver by a biopsy obtained through the peritoneoscope were carried out. Recognition of his contributions was signalized in the award of a Bronze Star in 1945. He published numerous articles, largely concerning liver disease. After his return from the Army, a unique technic of obtaining a cholecystogram and cholangiogram was developed. Radiopaque solutions were injected into the gall bladder through a needle which traversed the abdominal wall and was inserted into the gall bladder by peritoneoscopic visualization. His various studies were attended by a remarkably low rate of complications.

His fellow practitioners in Detroit will remember him as a capable consultant and advisor, and many of them are grateful for the attention given them when they were his patients. The loss suffered by his surviving wife and two young children is shared by his multitude of close professional friends.

G. Thomas McKean, M.D., F.A.C.P.

DR. EDWARD PAUL LEEPER

Dr. Edward Paul Leeper, F.A.C.P., of Dallas, Texas, died suddenly on February 9, 1952. Dr. Leeper was born in Denison, Texas, June 30, 1903. After attending public schools in Denison, he entered the University of Texas and received a Bachelor of Arts degree in 1924. He was graduated from the University of Texas School of Medicine in 1928. After serving his internship in St. Luke's Hospital in Chicago, Ill., Dr. Leeper became an assistant resident in medicine at Billings Hospital, University of Chicago.

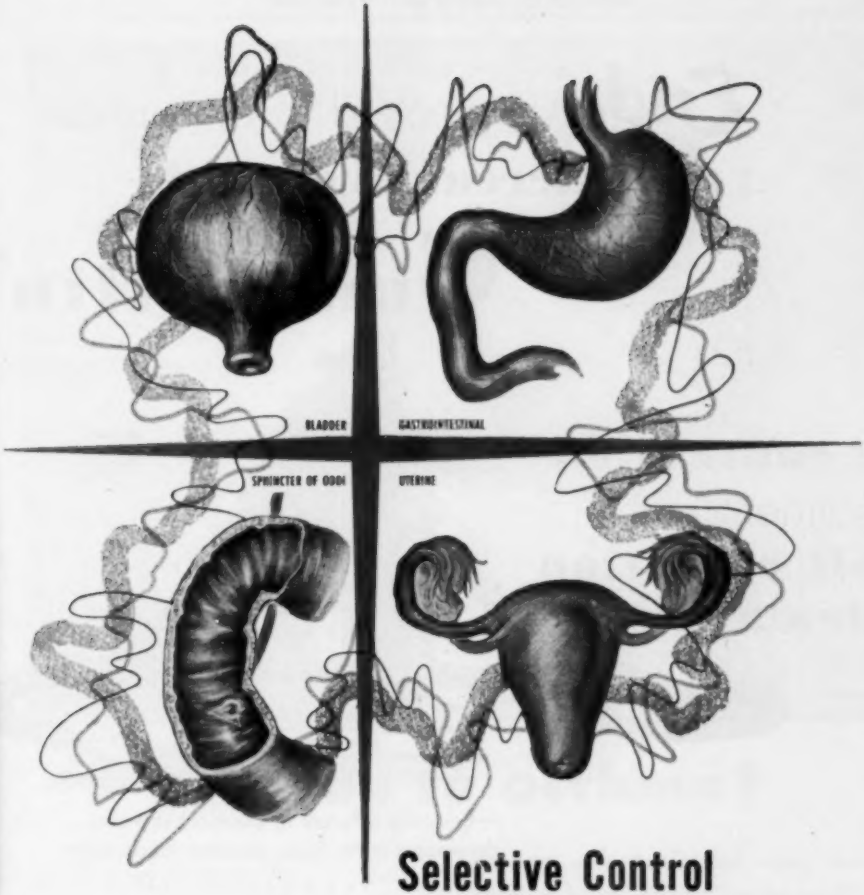
Dr. Leeper entered upon the private practice of internal medicine in Dallas in 1931 and became associated with Baylor University College of Medicine as Assistant in Clinical Medicine. In 1938 he was promoted to Assistant Professor of Clinical Medicine and held this post until he entered the Medical Corps, Army of the United States, in June of 1943. He served in the Medical Corps until 1946. He was post surgeon at the station hospital of Hondo Army Air Field, Hondo, Texas. At the time of his separation from the service, he held the rank of Colonel and had been in the Reserves since then.

Upon returning to civilian life, Dr. Leeper became Associate Professor of Clinical Medicine at the Southwestern Medical School of the University of Texas and he occupied this position until his death. He was a Fellow of the American Medical Association and also a member of his state and local medical societies. He was a member of the American Heart Association, American Diabetes Association, and the Texas Club of Internists. He was elected a Fellow of the American College of Physicians in 1942.

He assumed the duties of health officer for the City of University Park, Texas, in 1931 and served continuously in that post except for the time spent in military service during World War II. For many years he was medical director of the Praetorian Life Insurance Company.

Dr. Leeper served a large clientele effectively and was a man of broad civic interests.

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas



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